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CONTENTS

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JAN VAN BREEMEN, 1875-1961

The Nederlandse Vereniging van Rheumatologen regret to announce the death of their founder and honorary member, Jan van Breemen.

He died, after a short illness, at the age of 86 years, in his beloved city of Amsterdam, the freedom of which has been bestowed upon him many years ago.

In youth, he had desired to become a naval officer, but was refused owing to defective eyesight, a fact which, in years to come, he used to mention with an ironic smile, adding: " . . . and that's why, in the whole of my life, I have never had to wear glasses".

Nevertheless, he proved a true master mariner, exploring undiscovered provinces in rheumatology, letting his eyes sweep over vast horizons. A sailor at heart, he looked upon the entire world as his domain. Although a citizen of a small nation, he succeeded in uniting rheumatologists—in small numbers at the beginning—from all over the world: he was the founder and first secretary of the Ligue Internationale contre le Rhumatisme and of the Ligue Européenne contre le Rhumatisme. Even now there are few comparable international associations of medical specialists in existence.

Although no consummate linguist, he became a great orator through his love of truth, his originality in employing unorthodox manners of speech, and his personal charm.

Van Breemen was a loyal friend. From the walls of his study, which were hung with numerous portraits from many countries, the following motto greeted the visitor: "Of what can a man be proud if not of his friends."

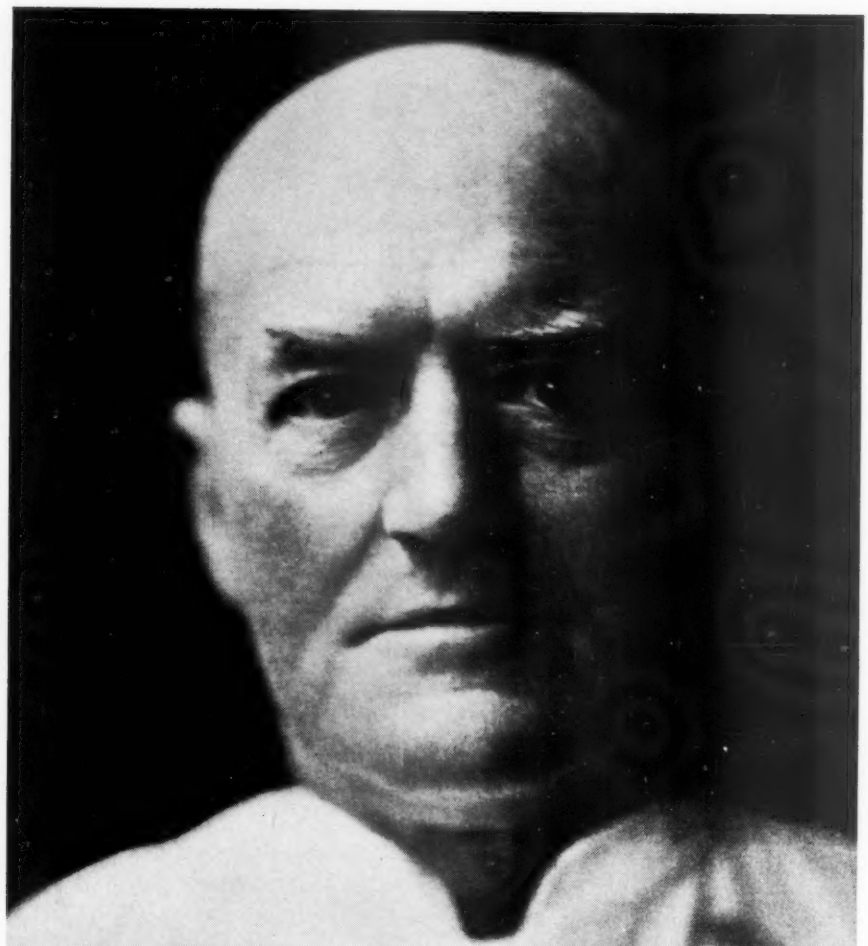
Conversely, we all felt honoured by the friendship of this remarkable man, whose every single action testified to his rare unselfishness.

From DR. W. H. D. DE HAAS, *Hon. Secretary,*

Amsterdam.

W.S.C.C. WRITES: Dr. van Breemen, in the course of his life-long pioneering campaign to get the rheumatic diseases officially noticed by the academic medical "Establishments", gathered round him a band of enthusiasts from many countries. This group has much diminished in recent years, and of the original members of the International Committee on Rheumatism which he and Dr. Fortescue Fox founded jointly in 1927, only Dr. Jacques Forestier and myself survive. This committee they reorganized in the following year as the Ligue Internationale contre le Rhumatisme. One of the League's first activities was to stimulate the formation of national committees, whilst the international journal *Acta Rheumatologica* was started under the editorship of van Breemen, and continued to appear until the outbreak of war in 1939. It was he who was eventually able to convince the leaders of governmental and academic medicine in European countries that, the battle against the acute infective diseases being nearly won, the chronic diseases—more particularly those embraced by the term "rheumatic"—must now be seriously approached

in the fields of both academic and sociological research. The Ligue Internationale held its sixth congress in England in 1938, and during a visit to Oxford Dr. van Breemen was presented with a fine Georgian bowl which had been subscribed for



JAN VAN BREEMEN

by every member of the British branch. His delighted and fluent speech of thanks, which it was subsequently realized had been given in English, was long remembered by those present.

Van Breemen is the father of modern rheumatology and his memory will always be honoured in this country where, as in many others, he was well loved.

Ann. Rheum. Dis. (1961), **20**, 117.

SULPHATE ($^{35}SO_4$) FIXATION BY HUMAN ARTICULAR CARTILAGE COMPARED IN THE KNEE AND SHOULDER JOINTS

BY

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The fixation of labelled sulphate ion, $^{35}SO_4$, is a measure of chondroitin-sulphate synthesis by cartilage cells, and a most satisfactory way of testing the viability of these cells (Curran and Gibson, 1956). In the case of human tissues, the test must be made *in vitro*, by incubating suitable slices of cartilage, obtained at biopsy or necropsy, in a medium containing a known amount of sulphur isotope, the uptake of which by the cells included in the cartilage sample can then be measured radiochemically and observed in autoradiographs.

McElligott and Collins (1960) used this technique to study human costal cartilage and the articular cartilage of the patella. Rib cartilage showed a high degree of sulphate utilization in infants, less in older children, and very little in the adult and elderly. In the articular cartilage, by contrast, sulphate utilization was found to increase as age advanced. It was concluded from the assays and from subsequent histochemical and autoradiographic studies (Collins and McElligott, 1960) that the increased avidity for sulphate in the older articular cartilages was related to the onset of osteo-arthritic cartilage fibrillation.

The influence of ageing, however, was not excluded as one of the causes of this rise in chondrocyte metabolism in the joint cartilages; most patellae of persons over 35 years of age show osteo-arthritic changes of some kind and aged non-arthritic cartilages are rare. In order to examine the effect of ageing alone on cellular function in articular cartilage, a study has now been made on paired specimens of cartilage from the patella and from the upper end of the humerus, since the shoulder joint, in contrast to the knee joint, seldom suffers from severe osteo-arthritis and is often free from pathological changes even at an advanced age (Heine, 1926).

Material

A shoulder joint and a knee joint on the same side, usually the left, were opened in the *post-mortem* room in the course of a number of randomly chosen necropsies on persons of either sex dying in the wards of the Royal Infirmary, Sheffield. The age at death ranged from 25 to 82 years. The upper end of the humerus and the whole of the patella were removed, and suitable preparations were made from them at once. If inspection of either joint showed any form of articular disease other than osteo-arthritis, the case was excluded from the study. Analyses were completed in 38 cases (Table I).

Methods

The articular surfaces were carefully inspected and the degree of osteo-arthritic change recorded. A central transverse block of each cartilage with underlying bone was taken; this after incubation in the sulphate medium provided material for histology and autoradiography. Adjoining blocks of cartilage stripped from the bone were taken and sliced finely before incubation for the purposes of quantitative assay of sulphate fixation.

The incubation medium was a salt solution containing buffered glucose and 4·8 mg. per litre of sulphate ions, as sodium sulphate (Kodicek and Loewi, 1955). To this was added approximately 5 microcuries (μc.) of ^{35}S per ml.

The radiochemical technique was that described in detail by McElligott and Collins (1960). Quantitative results are expressed as micrograms (μg.) of sulphate fixed per gram (g.) dried weight of cartilage. Control tests showed no significant uptake by boiled cartilage specimens. Autoradiographs were prepared as described by Collins and McElligott (1960), but were generally examined unstained or after light contrast staining with alcian green.

Grading of Osteo-Arthritis.—This followed that proposed by Collins (1949) and was based on naked-eye inspection of the joint surfaces supplemented by microscopical examination of the cartilage section.

Grade 0 Smooth cartilage surface.

Grade I Fibrillation of cartilage limited to the superficial zones of tangential and oblique fibres.

Grade II Fibrillation extending into the deep zone of vertical fibres, but no denudation of bone.

Grades III and IV Deep fibrillation with loss of cartilage exposing bare bone at one or more areas.

Results

Quantitative Results.—The results of the radiochemical assay in 38 paired specimens of cartilage from humerus and patella are all shown in Table I. Here the cases are grouped primarily according to the presence or absence of osteo-arthritis at the upper end of the humerus and secondarily according to the degree of osteo-arthritis at the patella. There is a considerable range of the numerical results from case to case; this is in line with our previous experience and is due, we believe, to biological variability, since the influence of technical factors has been controlled (McElligott and Collins, 1960). In any case, the important results in column 9 are expressed as a ratio of sulphate-fixing activity between paired specimens from the same individual processed in parallel.

Sex (Table I, col. 3) did not influence the results, a fact clearly shown in Table II.

TABLE II

SULPHATE FIXATION BY CHONDROCYTES OF ARTICULAR CARTILAGE OF HUMERUS AND PATELLA, BY SEX

Sex	Humerus		Patella	
	No. of Cases	Mean SO_4'' Uptake (μg./g.)	No. of Cases	Mean SO_4'' Uptake (μg./g.)
Male ..	22	1·055	22	0·973
Female ..	16	1·052	16	1·008

TABLE I

CHONDROCYTE ACTIVITY (EXPRESSED AS μg. SO_4'' TAKEN UP BY 1 g. DRIED CARTILAGE) OF ARTICULAR CARTILAGE OF UPPER END OF HUMERUS AND OF PATELLA IN 38 CASES AND THE RATIO OF ACTIVITY IN THE TWO CARTILAGES (EXPRESSED AS PATELLA/HUMERUS)

Specimen No.	Age of Patient (yrs)	Sex	Time after Death (hrs)	Humerus		Patella		P/H Uptake Ratio
				Grade of Osteo-arthritis	SO_4'' Uptake (μg./g.)	Grade of Osteo-arthritis	SO_4'' Uptake (μg./g.)	
R20	25	M	19	0	0·278	0	0·126	0·45
R28	30	F	13	0	1·568	0	1·039	0·66
R31	45	M	22	0	0·839	0	0·931	1·11
R34	37	F	23	0	1·603	0	0·995	0·62
R38	37	F	23	0	0·710	0	0·434	0·61
R45	33	F	21	0	1·364	0	1·004	0·74
R10	63	M	15	0	1·979	I	1·115	0·56
R15	35	M	22	0	0·425	I	0·353	0·83
R17	42	F	21	0	1·707	I	1·811	1·06
R23	63	M	24	0	0·493	I	0·453	0·92
R24	43	M	24	0	0·605	I	0·225	0·37
R30	50	M	6	0	0·165	I	0·247	1·50
R39	39	F	15	0	0·708	I	0·725	1·02
R41	60	M	7	0	2·132	I	1·223	0·57
R43	53	F	17	0	1·020	I	1·201	1·18
R 2	65	F	12	0	0·557	II	0·704	1·26
R 3	62	M	14	0	0·394	II	0·505	1·28
R 5	59	F	6	0	1·274	II	1·658	1·30
R 7	49	M	14	0	1·487	II	1·235	0·83
R11	66	F	10	0	1·342	II	0·648	0·48
R13	59	M	22	0	1·607	II	1·449	0·90
R18	74	F	11	0	0·436	II	0·366	0·84
R19	72	M	25	0	1·780	II	1·644	0·92
R25	60	M	8	0	1·627	II	0·528	0·32
R27	73	M	8	0	0·462	II	1·131	2·45
R35	53	M	19	0	0·534	II	1·925	3·60
R 4	75	M	21	0	2·117	III-IV	2·278	1·08
R21	70	F	12	0	0·467	III-IV	1·036	2·22
R29	68	F	24	0	0·580	III-IV	1·620	2·80
R14	52	M	22	I	0·286	I	0·212	0·74
R16	39	M	25	I	1·287	I	1·298	1·01
R33	72	M	16	I	0·370	II	0·983	2·66
R36	80	M	9	I	1·188	II	0·817	0·69
R37	74	M	17	I	1·762	II	1·537	0·87
R 6	67	F	21	I	0·435	III-IV	0·569	1·31
R12	80	F	10	I	1·946	III-IV	1·531	0·79
R40	71	F	5	I	1·116	III-IV	0·793	0·71
R44	82	M	15	I	1·382	III-IV	1·200	0·87

The time after the patient's death at which incubation of the cartilage was started (Table I, col. 4) ranged from 5 to 25 hours. The activity of cartilage does deteriorate when retained in the body after death, partly because of the slow rate of cooling and partly because it remains in contact with perichondrial tissues. McElligott and Collins (1960) have considered these influences and found that measurable amounts of sulphate can still be fixed by cartilage not excised until 36 hours after death. No statistical relationship exists in Table I between the length of time after death that the cartilage was collected and the result of the individual radiochemical assay. We assume that external influences would have affected the patella and humerus cartilages equally and that the P/H ratio in Table I, col. 9, is therefore valid.

The influence of the presence of varying degrees of osteo-arthritis on the results is shown in Table III. Osteo-arthritis of Grades II, III, or IV, which was encountered only in the patella, enhances the activity of the chondrocytes in utilizing sulphate. This is in accord with the results of Collins and McElligott (1960), who concluded that the increasing avidity for sulphate in increasing grades of osteo-arthritis was a cellular function representing a stimulation of cells to manufacture chondroitin sulphate in response to the loss of the surrounding matrix. No greater severity of osteo-arthritis than Grade I was seen in the shoulder joint in this series; in every case the main depth of the cartilage was intact and, indeed, the destruction of cartilage was in all but one instance no more extensive than a little superficial flaking along the tangential fibre lines.

The absence in the cartilage of the humerus of osteo-arthritic changes likely to stimulate chondrocytes to greater activity enables us to investigate the influence of age alone on the viability of articular cartilage cells. In Table IV the patients are collected into 20-year age groups. Age had no significant effect in the case of the humerus. In the case of the patella, the increase in the mean results with increasing age can be attributed to the frequent incidence of osteo-arthritis of severe grade in this cartilage (Table V).

TABLE V

INCIDENCE OF OSTEO-ARTHRITIC CHANGES OF VARYING SEVERITY IN 38 PAIRED SPECIMENS OF CARTILAGE FROM UPPER END OF HUMERUS AND PATELLA, BY 20-YEAR AGE GROUPS

Age (yrs)	Cartilage	Grades of Osteo-arthritis			
		0	I	II	III-IV
25-44	Humerus	9	1	0	0
	Patella	5	5	0	0
45-64	Humerus	12	1	0	0
	Patella	1	6	6	0
65-84	Humerus	8	7	0	0
	Patella	0	0	8	7

TABLE III

UPTAKE OF SULPHATE BY ARTICULAR CARTILAGE OF HUMERUS AND PATELLA *IN VITRO*, BY GRADE OF OSTEO-ARTHRITIS

Grade of Osteo-arthritis	Humerus			Patella		
	No. of Specimens	SO_4 Uptake (μg./g.)		No. of Specimens	SO_4 Uptake (μg./g.)	
		Mean	Range		Mean	Range
0	29	1·043	0·165–2·132	6	0·755	0·126–1·039
I	9	1·086	0·286–1·946	11	0·806	0·212–1·811
II	—			14	1·081	0·366–1·925
III-IV	—			7	1·290	0·569–2·278

TABLE IV

MEAN SULPHATE UPTAKE (μg./g.) OF ARTICULAR CARTILAGE FROM HUMERUS AND PATELLA, BY 20-YEAR AGE GROUPS IRRESPECTIVE OF OSTEO-ARTHRITIS GRADES

Age Range (yrs)	No. of Cases	Mean Age of Cases (yrs)	Humerus SO_4'' Uptake (μg./g.)		Patella SO_4'' Uptake (μg./g.)	
			Mean	Range	Mean	Range
25–44	10	36	1·026	0·278–1·707	0·801	0·126–1·811
45–64	13	56	1·064	0·165–2·132	0·976	0·212–1·925
65–84	15	73	1·063	0·370–2·117	1·124	0·366–2·278

Table I shows the P/H (patella/humerus) ratio of chondrocyte activity in the individual cases, but in Table VI the group P/H ratios are calculated from the mean uptake of each cartilage in the cases falling within the appropriate group.

TABLE VI

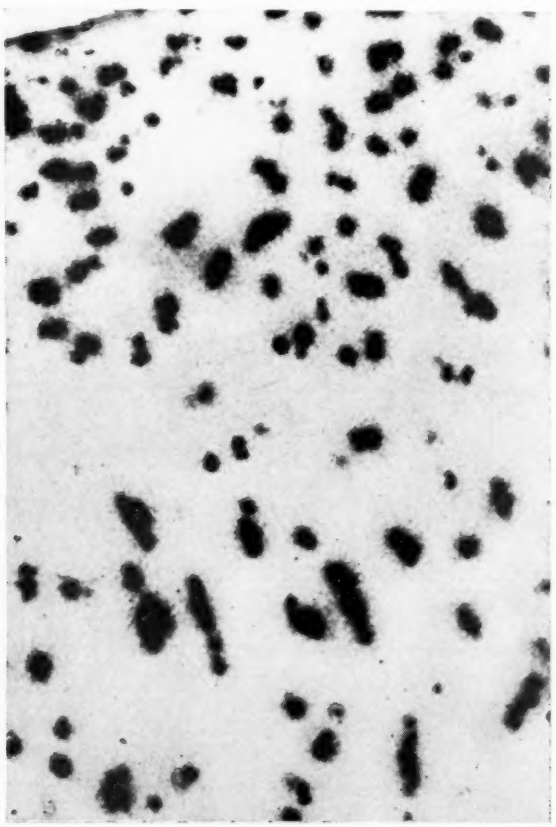
COMPARISON OF CHONDROCYTE ACTIVITY IN ARTICULAR CARTILAGES OF HUMERUS AND PATELLA BY GRADE OF OSTEO-ARTHRITIS AFFECTING THE PATELLA. RATIO OF MEANS (P/H) CALCULATED FROM THE SULPHATE-FIXING ACTIVITY OF EACH CARTILAGE

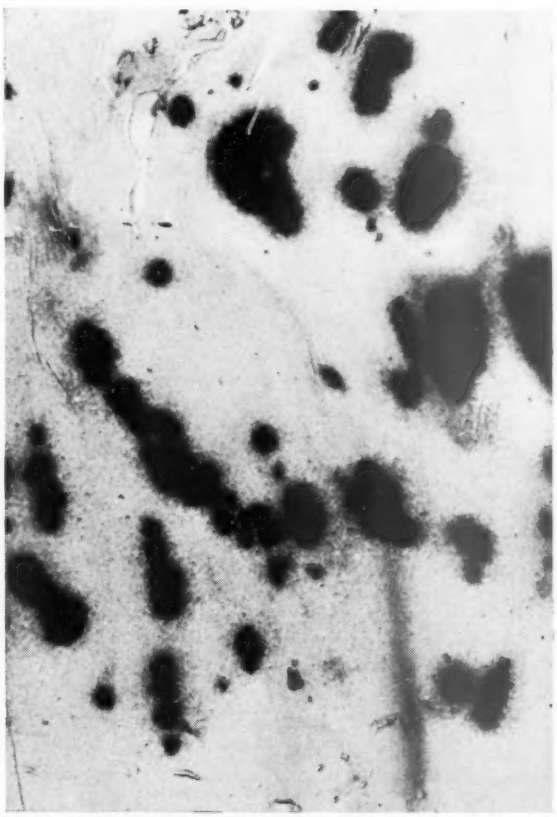
Grade of Osteo-arthritis		No. of Cases	P/H Ratio
Humerus	Patella		Mean sulphate uptake by patella / Mean sulphate uptake by humerus
0-I	0	6	0·71
	I	11	0·82
	II	14	1·01
	III-IV	7	1·12

It is clear that the patella cartilage tends to become more active than the humerus cartilage in sulphate utilization as soon as osteo-arthritic changes in the patella have advanced beyond Grade I, that is to the point where fibrillation has led to substantial loss of matrix and has stimulated a reactive synthesis of chondroitin sulphate by the cartilage cells. This enhancement of sulphate fixation by the osteo-arthritic cartilage of the patella as compared with the virtually unchanged cartilage of the humerus is the more noteworthy in that patellar cartilage showing only Grade I osteo-arthritis or none is evidently less biologically active than the humerus cartilage.

Autoradiographic Results.—Autoradiographs of sections of cartilage from humerus and patella were prepared in every case. Figs 1 and 2 illustrate the enhancement of chondrocyte activity with the onset of osteo-arthritis in the patella.

The autoradiographs also confirmed the obser-





Figs 1 and 2.—Autoradiographs showing sulphate ($^{35}SO_4$) uptake by chondrocytes of articular cartilage of humerus (Fig. 1) and patella (Fig. 2). Both specimens came from a woman aged 65 years and were processed in parallel. The shoulder joint was free from osteo-arthritis and the humerus cartilage is intact (Fig. 1). There was Grade II osteo-arthritis in the knee-joint and the patellar cartilage (Fig. 2) shows fibrillation, loss of matrix, and clumping of chondrocytes, with a dense radiographic shadow over each clump.
Radiochemical assay gave a sulphate uptake of 0·557 μg./g. for the humerus cartilage and 0·704 μg./g. for the patellar cartilage, and a P/H ratio of 1·26.
Autoradiographic exposure 60 days. Magnification of photo-micrographs ×100.

vations recorded by Collins and McElligott (1960), and they showed that the increased utilization of sulphate by osteo-arthritic cartilage is a function of the chondrocytes, particularly of those cells that proliferate to form multicellular clusters in the fibrillated area of the deep vertical-fibre zone. This appearance was, of course, seen only in the patella in our series of cases. In both the patella and the humerus, the cartilage cells of the superficial zones fixed little or no sulphate. The small cells very close to the surface of the intact cartilages seldom had granules over them, and those a little more deeply situated showed no reaction when there was tangential flaking as seen in the earliest (Grade I) phase of osteo-arthritis.

Summary and Conclusions

38 paired specimens of adult articular cartilage from the upper end of the humerus and from the patella were obtained from human autopsy material. Their ability to fix sulphate *in vitro*, using $^{35}SO_4$, was studied by radiochemical assay and autoradiography.

In the absence of osteo-arthritis, the cartilage from the patella tended to be less active in utilizing sulphate than that from the humerus. Grade I osteo-arthritis did not significantly increase this activity in either cartilage.

Osteo-arthritis of Grades II to IV, encountered only in specimens of patella, led to enhanced uptake of sulphate by the affected cartilage and to the situation in which, in paired specimens, the patellar cartilage became quantitatively more active than that from the humerus.

Autoradiographic studies confirmed the quantitative results and showed a heavy uptake of labelled sulphate by clumps of chondrocytes bordering the fissures of fibrillated osteo-arthritic cartilage.

The sex of the patient had no influence on the results.

In the case of cartilage from the humerus, the age of the patient did not affect the mean results. In the case of the patella, the increase of chondrocyte activity in older patients could not be dissociated from the increasing incidence of osteo-arthritis.

It is concluded, therefore, that the ability of the cells of adult human articular cartilage to synthesize sulphated mucopolysaccharides is uninfluenced directly by ageing. The enhancement of chondrocyte activity, seen for example in many specimens of patella with damaged cartilage, appears to be a reactive phenomenon to local conditions and the loss of mucopolysaccharide from the matrix associated with the process of osteo-arthritis within the affected joint.

The work here reported was performed with the aid of a research grant from the Empire Rheumatism Council for which we are very grateful.

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Fixation comparée du sulfate ($^{35}SO^4$) par le cartilage articular humain de l'épaule et par celui du genou

RÉSUMÉ

On obtint à l'autopsie 38 prélèvements appariés de cartilage articulaire humain adulte de l'extremité supérieure de l'humérus et de la rotule. Sa capacité pour fixer le sulfate *in vitro*, usant $^{35}SO^4$, fut étudiée par dosage radiochimique et par l'autoradiographie.

En l'absence d'ostéoarthrite, le cartilage rotulien tendait à absorber moins de sulfate que le cartilage huméral. La présence d'ostéoarthrite du grade I n'augmentait pas appréciablement l'activité des deux cartilages.

L'ostéoarthrite des grades II à IV, présente seulement dans les cartilages rotuliens, faisait augmenter l'absorption de sulfate par le cartilage affecté, produisant ainsi une situation où, lorsque les prélèvements venaient du même sujet, le cartilage rotulien devenait quantitativement plus actif que le cartilage humoral.

Les études autoradiographiques ont confirmé les résultats quantitatifs et indiqué une absorption considérable de sulfate marqué par les amas des chondrocytes bordant les fissures du cartilage fibrillaire ostéoarthritique.

Le sexe de la personne de laquelle provenait le cartilage n'avait aucune influence sur les résultats.

Pour le cartilage huméral, l'âge de la personne n'affectait pas les résultats moyens. Pour la rotule, l'augmentation de l'activité des chondrocytes avec l'âge ne pouvait pas être dissociée de la fréquence croissante d'ostéoarthrite.

On conclut que la capacité du cartilage articulaire humain pour synthétiser des mucopolysaccharides sulfatés n'est pas affectée directément par l'âge. L'augmentation de l'activité chondrocytaire, observée, par exemple, dans les prélèvements de cartilage rotulien lésé, semble être un phénomène de réaction contre des conditions locales et la perte des mucopolysaccharides de la matrice, associée au processus d'ostéoarthrite dans l'articulation affectée.

Comparación de la fijación de sulfato radioactivo ($^{35}SO^4$) por el cartílago articular humano del hombro y por él de la rodilla

SUMARIO

Se obtuvieron en autopsia 38 muestras apareadas de cartílago articular humano adulto procedentes del cabo superior del húmero y de la rótula. Se estudió radioquímicamente y por autorradiografía su capacidad para fijar sulfato *in vitro*, usando $^{35}SO^4$.

En ausencia de osteoartritis, el cartílago rotuliano tendía a ser menos activo en la utilización del sulfato que aquel procedente del húmero. Presencia de osteoartritis del grado I no aumentaba significativamente la actividad de ninguno de ambos cartílagos.

Osteoartritis de grados II a IV, presente solamente en cartílagos rotulianos, produjo incremento en la absorción de sulfato por el cartílago afecto, creando una situación en que, en muestras procedentes del mismo individuo, el cartílago rotuliano fué cuantitativamente más activo que el humoral.

Estudios autorradiográficos confirmaron los resultados cuantitativos y mostraron una considerable absorción de sulfato marcado en los acúmulos de condrocitos bordeando las fisuras del cartílago fibrilar osteoartrítico.

El sexo de la persona a quien pertenecía el cartílago no tuvo influencia alguna.

En el caso del cartílago humeral, la edad de la persona no afectó los resultados medios. En el caso del cartílago rotuliano, el aumento de actividad condrocítica con la edad no pudo separarse de la creciente incidencia de osteoartritis.

Se concluye que la habilidad del cartílago articular humano para sintetizar mucopolisacaridos sulfatados no es directamente afectada por la edad. El aumento de la actividad condrocítica, observada por ejemplo en muchas de las muestras de cartílago rotuliano lesionado, parece ser un fenómeno reactivo a condiciones locales y a pérdida de mucopolisacaridos de la matriz, asociada con procesos osteoartríticos dentro de la articulación afectada.

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PSORIATIC ARTHRITIS

A COMPARATIVE RADIOGRAPHIC STUDY OF RHEUMATOID ARTHRITIS AND ARTHRITIS ASSOCIATED WITH PSORIASIS

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Attention was focused on the association of psoriasis and arthritis by Alibert (1822), and the first detailed examination of the relation between the two was that of Bourdillon (1888). Since then there has been much interest in and argument about psoriatic arthritis. Definitions of the condition have been various: an arthritis confined to the distal interphalangeal joints associated with psoriasis (Bauer, Bennett, and Zeller, 1941), an atypical arthritis associated with atypical psoriasis (Dawson, 1937), and a form of atrophic arthritis associated with psoriasis exhibiting a reasonable amount of synchronous activity as evidenced by remissions and relapses in arthritis and cutaneous manifestations (Epstein, 1939; Jeghers and Robinson, 1937; Lane and Crawford, 1937). Other authors have denied its existence as a separate entity, feeling that it represented the coincidence of two common diseases, psoriasis and rheumatoid arthritis (Brocq, 1910; Gribble, 1955; Margolis, 1941). Recently, workers with the Rose-Waaler differential agglutination test (D.A.T.), which is positive in about 80 per cent. of patients with rheumatoid arthritis (Greenbury, Hill, Spalding Smith, and Good, 1956; *Brit. med. J.*, 1956; Wright, 1957c), have noted that, in those patients who had psoriasis with atrophic arthritis, the test was usually negative (Ball, 1952; Coste, 1958; Coste and others, 1958; de Forest, Mucci, and Boisvert, 1956; Jacobson, Kammerer, Wolf, Epstein, and Heller, 1956; Ziff, 1957), as was the latex-fixation test (Reed and Becker, 1960). From a previous study of 39 patients with psoriasis and arthritis, it was suggested that those patients who had a negative D.A.T. either had rheumatoid arthritis modified by the presence of psoriasis, or (more likely) were suffering from a different and distinct condition (Wright, 1956, 1957b).

Radiographically, the interest in this condition is reflected by the recent publication of single cases and small series (Carrier, 1958; Meaney and Hays, 1957; Reed and Becker, 1960). Good reviews of the subject have been published by Fawcitt (1950) and Sherman (1952), but surveys of the general field of psoriasis and joint disease have been few. A retrospective analysis has been done at the Mayo Clinic, but no prospective study was undertaken (Avila, Pugh, Slocumb, and Winkelmann, 1960). In a previous report (Wright, 1957a), the radiographic features of psoriatic arthritis were discussed, but the number of patients was too small for statistical analysis and no control series of patients with uncomplicated rheumatoid arthritis was studied. The series has therefore been extended and comparison made with patients with rheumatoid arthritis.

Material and Methods

157 patients with psoriasis and various rheumatic complaints have been considered, of whom 121 had erosive arthritis. 91 of the patients with psoriasis and erosive arthritis were paired with patients of the same sex and age who had uncomplicated rheumatoid arthritis of the same duration and had a positive D.A.T. Radiographs of the hands, feet, and sacro-iliac joints were taken. The films of the sacro-iliac joints in four patients with psoriatic arthritis and one with rheumatoid arthritis, and of the feet in two patients with psoriatic arthritis and one with rheumatoid arthritis were not available for study. The films were read without the name or diagnosis of the patients being known.

The D.A.T. was done by a modification of existing techniques (Heller, Kolodny, Lepow, Jacobson, Rivera, and Marks, 1955; Rose, Ragan, Pearce, and Lipman, 1948; Waaler, 1940) introduced by Greenbury and others (1956).

General Review of Results

The composition of the series is shown in Table I. Patients with osteo-arthritis, gout, rheumatic fever, and muscular rheumatism showed no atypical clinical or radiographic features and their association seemed fortuitous.

TABLE I

COMPOSITION OF SERIES WITH PSORIASIS AND RHEUMATIC COMPLAINTS

Diagnosis	Sex		
	Male	Female	Total
Erosive Arthritis	42	79	121
Osteo-arthritis	9	14	23
Gout	2	0	2
Rheumatic Fever	2	0	2
Muscular Rheumatism ..	5	4	9
Total	59	95	157

Of the 121 patients with psoriasis and erosive arthritis, eighteen had a positive D.A.T. The clinical findings in these were the same as in the group with uncomplicated rheumatoid arthritis. Subcutaneous nodules were present in four, an incidence similar to that in rheumatoid arthritis both in this and other series (Bauer, 1939; Short, Bauer, and Reynolds, 1957). There was no significant difference in the radiographic features of the arthritis compared with uncomplicated rheumatoid arthritis, and these patients were considered as examples of coincidental rheumatoid arthritis.

The clinical picture of 103 patients (33 men, 70 women) with psoriasis and erosive arthritis with a negative D.A.T. differed from uncomplicated rheumatoid arthritis and has been described elsewhere (Wright, 1959). There were differences also in the radiographic appearances. The term "psoriatic arthritis" has been used for patients with psoriasis and erosive arthritis with a negative D.A.T. In this analysis the group with psoriatic arthritis has been compared with uncomplicated rheumatoid arthritis and coincidental rheumatoid arthritis and psoriasis.

Hands and Feet

Distal Interphalangeal Joints.—The findings in the interphalangeal joints of the thumbs and big toes were analysed separately from other distal joints, as their exact status was uncertain. There was no significant difference in loss of space, erosion, or expansion of the base of the terminal phalanx in these joints in psoriatic arthritis compared with rheumatoid arthritis. However, erosion of the interphalangeal joints of the thumbs, compared with erosion of the proximal interphalangeal joints, was commoner in psoriatic arthritis than in rheumatoid arthritis (Tables II and III).

In the distal joints of other fingers, erosion was more common in psoriatic arthritis than rheumatoid arthritis (Table II). Changes in psoriatic arthritis (Figs 1 and 2, opposite) were usually more gross than in rheumatoid arthritis. In only one patient with psoriatic arthritis was arthritis limited to the distal joints. The distal joints of the toes were involved more often ($P < 0{\cdot}01$) in psoriatic arthritis than uncomplicated or coincidental rheumatoid arthritis.

Terminal Phalanges.—Changes in the terminal phalanx, although uncommon, were characteristic of psoriatic arthritis. They included cystic areas and irregularity of the tip extending to the shaft, progressing to whittling away of the bone (Fig. 2).

TABLE II

RADIOGRAPHIC FINDINGS IN THE DISTAL INTERPHALANGEAL JOINTS OF THE FINGERS AND TOES

Digit	Finding	Psoriatic Arthritis (103 patients)	Rheumatoid Arthritis (91 patients)	Coincidental Rheumatoid Arthritis (18 patients)
Thumb	Loss of space	17	10	—
	Erosion	18	11	2
	Expanded base of T.P.	12	3	—
	Ankylosis	2	—	—
Second to Fifth Fingers	Loss of space	18	16	2
	Erosion	23	11	3
	Expanded base of T.P.	12	4	1
	Ankylosis	3	—	—
Big Toe	Erosion	18	3	1
Second to Fifth Toes	Erosion	18	2	2

TABLE III

RADIOGRAPHIC FINDINGS IN THE PROXIMAL INTERPHALANGEAL JOINTS OF THE FINGERS AND TOES

Site	Finding	Psoriatic Arthritis (103 patients)	Rheumatoid Arthritis (91 patients)	Coincidental Rheumatoid Arthritis (18 patients)
Hands	Loss of space	17	38	8
	Erosions	30	45	8
	Cysts	6	7	1
	Ankylosis	1	4	1
Feet	Erosions	23	15	3

In the fingers cystic changes occurred in four patients, whittling in two. In the toes, whittling occurred in five and irregularity of the shaft in fifteen, but in only three patients with rheumatoid arthritis ($P < 0{\cdot}01$). Whittling away of the bone occurred only in association with nail changes. Radiographs of the hands and feet of fourteen patients with severe psoriatic nail changes and no clinical evidence of arthritis were therefore taken, but no changes in the terminal phalanges were seen.

Opacities in the terminal phalanges of the fingers were noted in fifteen patients with psoriatic arthritis and in thirteen with rheumatoid arthritis. In the

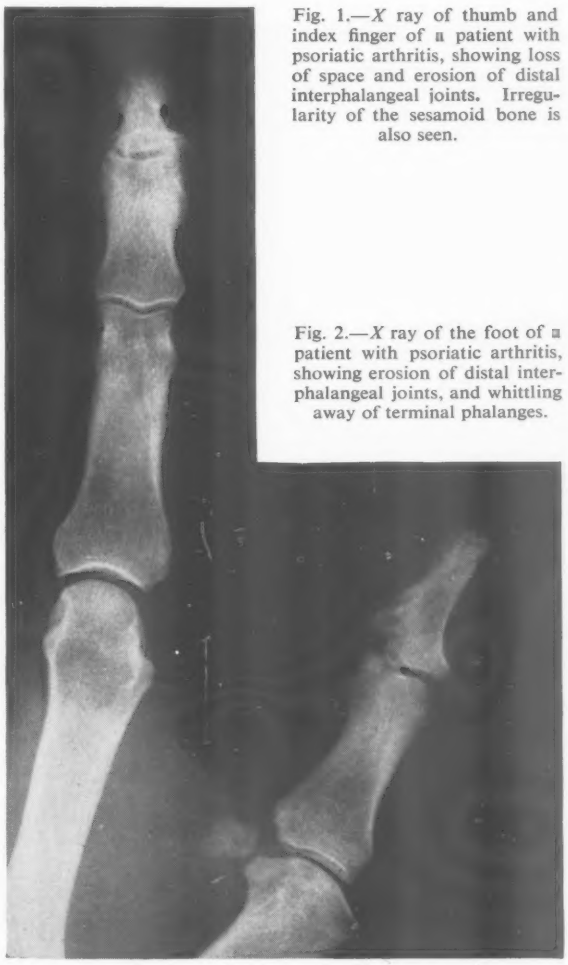
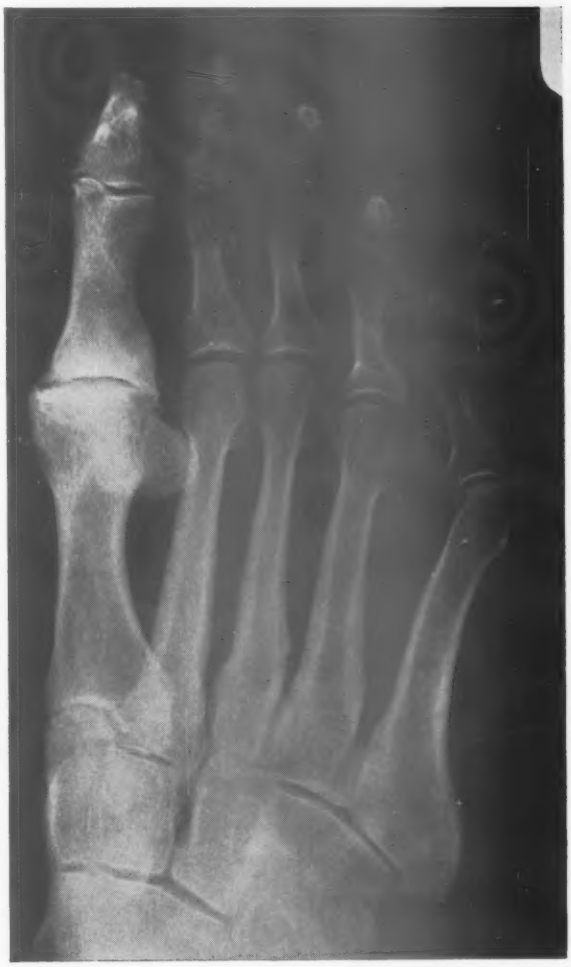


Fig. 1.—*X* ray of thumb and index finger of a patient with psoriatic arthritis, showing loss of space and erosion of distal interphalangeal joints. Irregularity of the sesamoid bone is also seen.

Fig. 2.—*X* ray of the foot of a patient with psoriatic arthritis, showing erosion of distal interphalangeal joints, and whittling away of terminal phalanges.



rheumatoid group the changes were noted only in women (a sex difference of probable significance, $P < 0{\cdot}05$). In psoriatic arthritis they occurred in twelve women and three men.

Other Digital Joints.—In the proximal interphalangeal joints of the toes, only the erosions were read since loss of space is difficult to ascertain in these joints. There was no significant difference between the groups, although involvement was commoner in psoriatic arthritis (Table III, and Fig. 3).

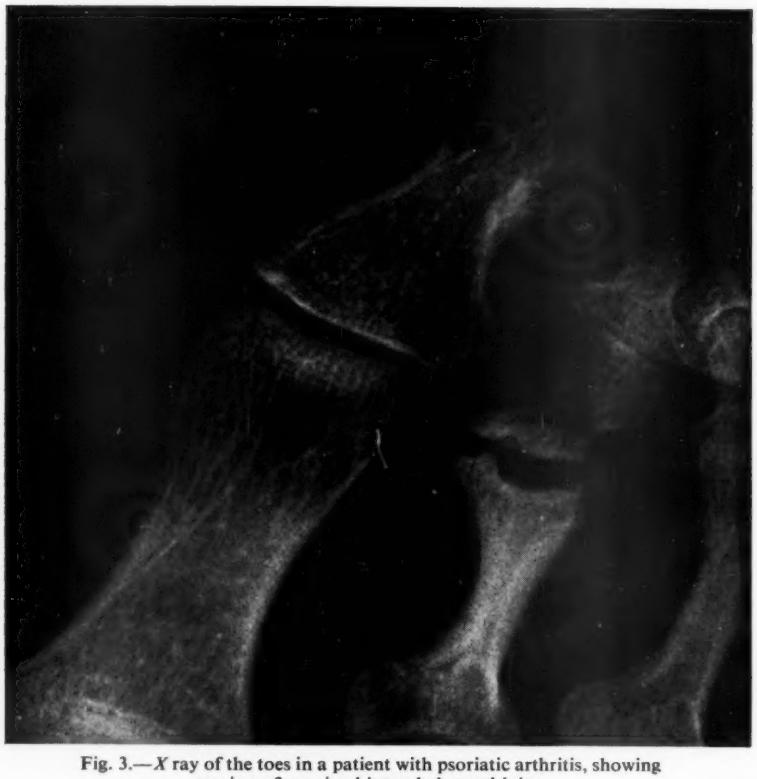


Fig. 3.—*X* ray of the toes in a patient with psoriatic arthritis, showing erosion of proximal interphalangeal joint.

Loss of space and erosion in the proximal interphalangeal joints of the fingers were more common in rheumatoid arthritis than psoriatic arthritis ($P < 0{\cdot}01$). In the metacarpo-phalangeal and metatarso-phalangeal joints loss of space and erosions were commoner in rheumatoid arthritis than psoriatic arthritis (Table IV, $P < 0{\cdot}01$). There features were significantly commoner ($P < 0{\cdot}01$) in the metatarso-phalangeal joints of patients with coincidental rheumatoid arthritis than with psoriatic arthritis. Deformity of the metacarpo-phalangeal joints was commoner in uncomplicated and coincidental rheumatoid arthritis ($P < 0{\cdot}01$ and $< 0{\cdot}05$).

Wrists.—In the carpus, loss of space and erosion were commoner ($P < 0{\cdot}01$) in uncomplicated and coincidental rheumatoid arthritis (Table V, opposite). Ankylosis was significantly commoner in uncomplicated rheumatoid arthritis ($P < 0{\cdot}01$).

The radio-navicular joint (Table V) similarly showed loss of space and erosion more often in uncomplicated and coincidental rheumatoid arthritis ($P < 0{\cdot}01$), and ankylosis significantly more often in uncomplicated rheumatoid arthritis ($P < 0{\cdot}02$).

We were unable to confirm the suggestion that there is a relative sparing of the metacarpo-phalangeal joints when the wrists are involved in psoriatic arthritis. The metacarpo-phalangeal joints were usually involved to a greater degree than the wrists in rheumatoid arthritis and psoriatic arthritis. In only six psori-

TABLE IV

RADIOGRAPHIC FINDINGS IN THE METACARPO- AND METATARSO-PHALANGEAL JOINTS

Site	Finding	Psoriatic Arthritis (103 patients)	Rheumatoid Arthritis (91 patients)	Coincidental Rheumatoid Arthritis (18 patients)
Hands	Loss of space	25	57	7
	Erosions	24	57	8
	Cysts	3	9	2
	Deformity	10	19	6
Feet	Loss of space	15	49	10
	Erosions	24	62	10
	Cysts	8	11	4
	Deformity	17	35	2

TABLE V
RADIOGRAPHIC APPEARANCES IN THE WRISTS

Site	Finding	Psoriatic Arthritis (103 patients)	Rheumatoid Arthritis (91 patients)	Coincidental Rheumatoid Arthritis (18 patients)
Carpus	Loss of space	16	35	6
	Erosions	18	52	9
	Ankylosis	6	17	3
Radio-navicular	Loss of space	18	48	8
	Erosions	19	45	9
	Ankylosis	6	16	3
Ulnar Styloid Erosion		22	42	8
Radio-ulnar Involvement		14	41	8

TABLE VI
DEGREE OF INVOLVEMENT OF METACARPOPHALANGEAL JOINTS (M.P.) and WRISTS AND RELATIVE FREQUENCY OF INVOLVEMENT OF RADIO-ULNAR AND RADIO-NAVICULAR JOINTS

Degree of Joint Involvement	Psoriatic Arthritis (103 patients)	Rheumatoid Arthritis (91 patients)	Coincidental Rheumatoid Arthritis (18 patients)
M.P. > Wrists	19	28	2
Wrists > M.P.	6	12	2
M.P. = Wrists	12	31	6
Neither Involved	66	20	8
Radio-ulnar Only	3	4	1
Radio-navicular Only	7	17	1
Both	12	33	7
Neither	81	37	9

atic patients was the reverse true (Table VI).

The radio-ulnar joint was involved more often in uncomplicated and coincidental rheumatoid arthritis ($P < 0{\cdot}01$), but it was not found that where the wrists were involved it was the radio-ulnar rather than the radio-navicular joint which was affected in psoriatic arthritis (Table VI). The ulnar styloid process frequently showed erosion in all groups (Table V), but was more often involved in uncomplicated and coincidental rheumatoid arthritis ($P < 0{\cdot}01$). It was of interest that in ten patients with rheumatoid arthritis the ulnar styloid process was eroded without evident damage of the radio-navicular joint. Involvement of this process is a useful sign of rheumatoid arthritis.

Sacro-iliac Joints

The radiographic findings in the sacro-iliac joints of the present series are shown in Table VII.

TABLE VII
RADIOGRAPHIC APPEARANCES IN SACRO-ILIAC JOINTS

Finding	Psoriatic Arthritis (99 patients)	Rheumatoid Arthritis (90 patients)	Coincidental Rheumatoid Arthritis (18 patients)
Erosion ..	19	5	1
Sclerosis ..	11	4	1
Ankylosis ..	8	1	1

Erosion was more common in psoriatic arthritis ($P < 0{\cdot}01$). Sclerosis and ankylosis (Fig. 4, overleaf) were also more common in psoriatic arthritis. In only one patient with uncomplicated rheumatoid arthritis did ankylosis occur, and this was present on one side only. Unilateral changes occurred in six of the 29 patients with psoriatic arthritis who had sacro-iliac involvement. The proportion of unilateral changes were not significantly different in rheumatoid arthritis.

Other Features

A severely destructive arthritis occurred in four patients with psoriatic arthritis. They showed classical arthritis mutilans with *main en lorgnette* (opera-glass hand) and a similar condition in the feet. There was "melting away" of the metatarsal and metacarpal heads and phalanges (Figs 5 and 6, overleaf). In all four the sacro-iliac joints were also involved.

Some authors have commented on a lack of bone porosis despite destruction, but in the present series this feature was only noted in three patients with psoriatic arthritis and one with rheumatoid arthritis. A generalized osteoporosis, however, was found more commonly in the hands and feet of patients with uncomplicated rheumatoid arthritis.

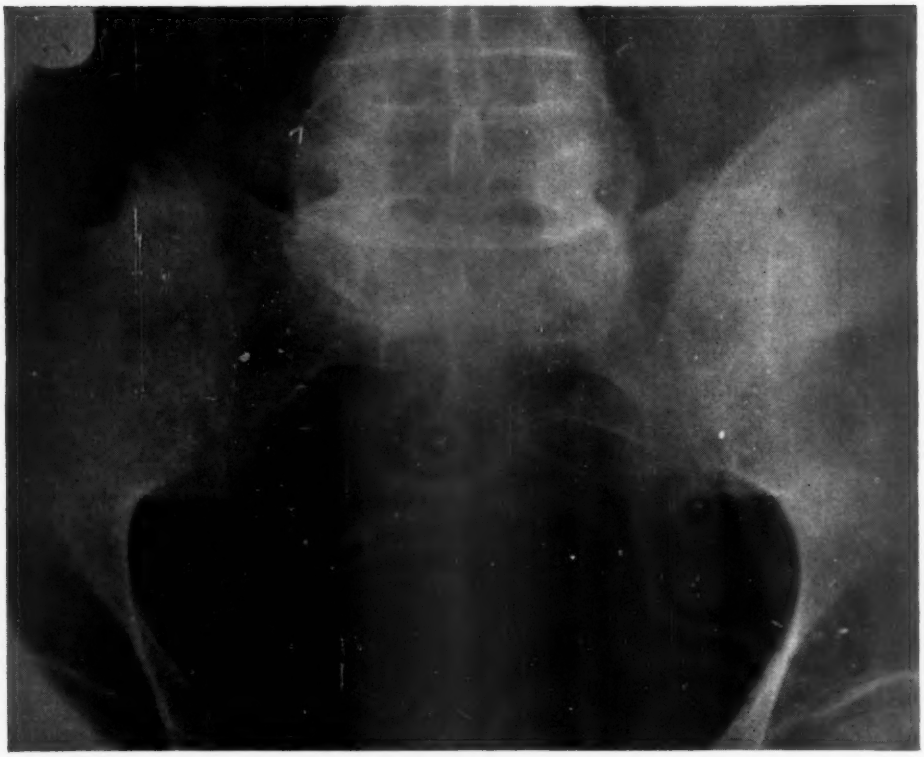


Fig. 4.—*X* ray of the sacro-iliac joints of a patient with psoriatic arthritis, showing ankylosis.

Only in the metatarso-phalangeal joints of patients with psoriatic arthritis was asymmetrical involvement found. Such asymmetry was seen in 42 per cent. of psoriatic patients with these joints involved compared with 18 per cent. of rheumatoid patients ($P < 0{\cdot}02$).

Discussion

Definition

The absence until recent years of a laboratory test which would distinguish between rheumatoid arthritis and psoriatic arthritis has made analysis of the clinical and radiographic features of psoriatic arthritis difficult. The advent of the Rose-Waaler differential agglutination test (D.A.T.) seems to have provided a solution, for this detects a specific abnormality in the serum of about 80 per cent. of patients with rheumatoid arthritis (Ball, 1952).

Of 121 patients with psoriasis and erosive arthritis, eighteen had a positive D.A.T. Their clinical and radiographic picture differed in no way from that of uncomplicated rheumatoid arthritis, and they appear to be examples of coincidental psoriasis and rheumatoid arthritis, an association one would expect to find in an unselected series since both diseases are common. This view is strengthened by the finding in these patients of subcutaneous nodules, often regarded as the most characteristic lesion of rheumatoid arthritis (Bauer, 1939; Bennett, 1943), in a proportion similar to that seen in patients with uncomplicated rheumatoid arthritis, whilst in psoriatic patients with a negative D.A.T. they were absent. In our present state of knowledge it would seem wisest to designate as "psoriatic arthritis" the erosive arthritis in psoriatic patients with a negative D.A.T. The finding of a group of patients with coincidental rheumatoid arthritis in a large unselected series is important, not only because it confirms what would be anticipated if psoriatic arthritis is a separate entity, but also because it provides a group for comparative purposes. It is interesting to note, therefore, that, although the group was usually too small to permit statistical comparisons, the differences between uncomplicated rheumatoid arthritis and psoriatic arthritis were similar in the patients with coincidental rheumatoid arthritis. Since some patients with psoriatic arthritis when examined individually have an arthritis very similar to rheumatoid arthritis, and arthritis may precede the psoriasis by many years, it has

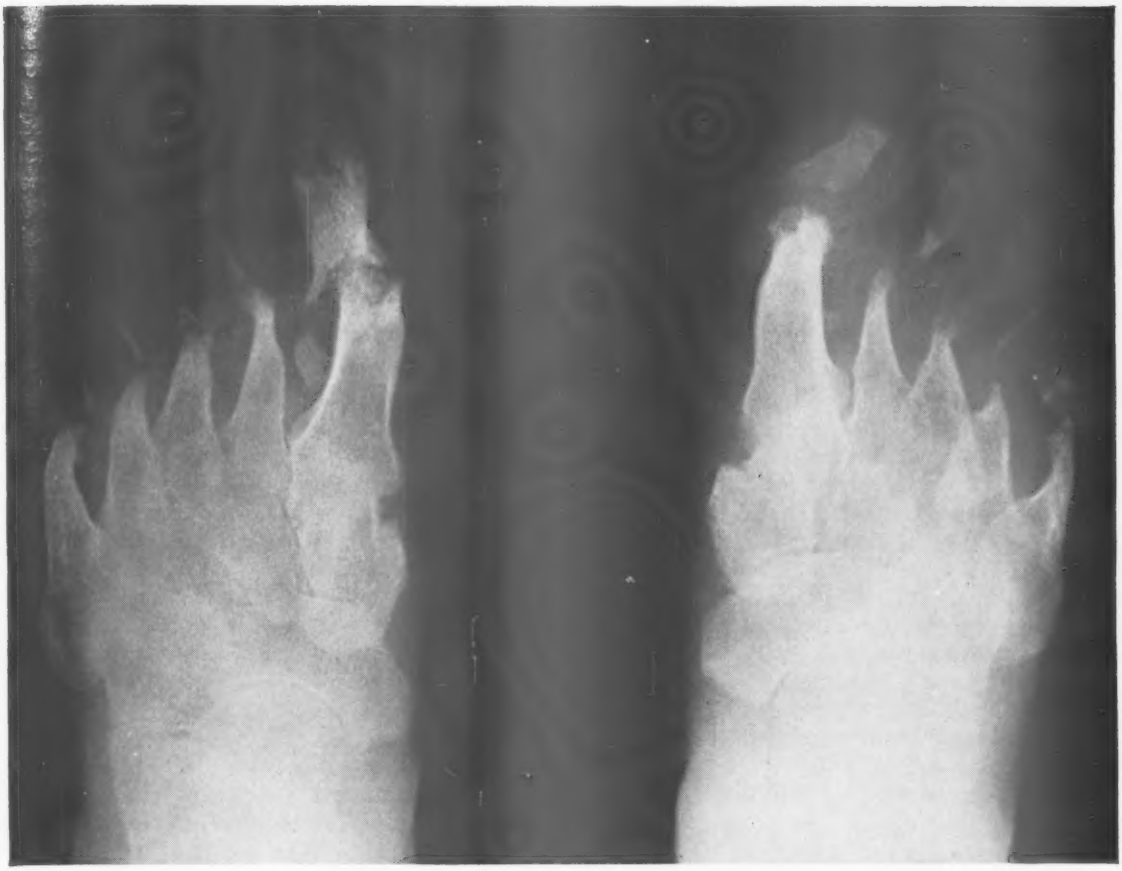


Fig. 5.—*X* ray of the feet of a man with psoriatic arthritis, showing tapering of metatarsal bones and destruction of phalanges.

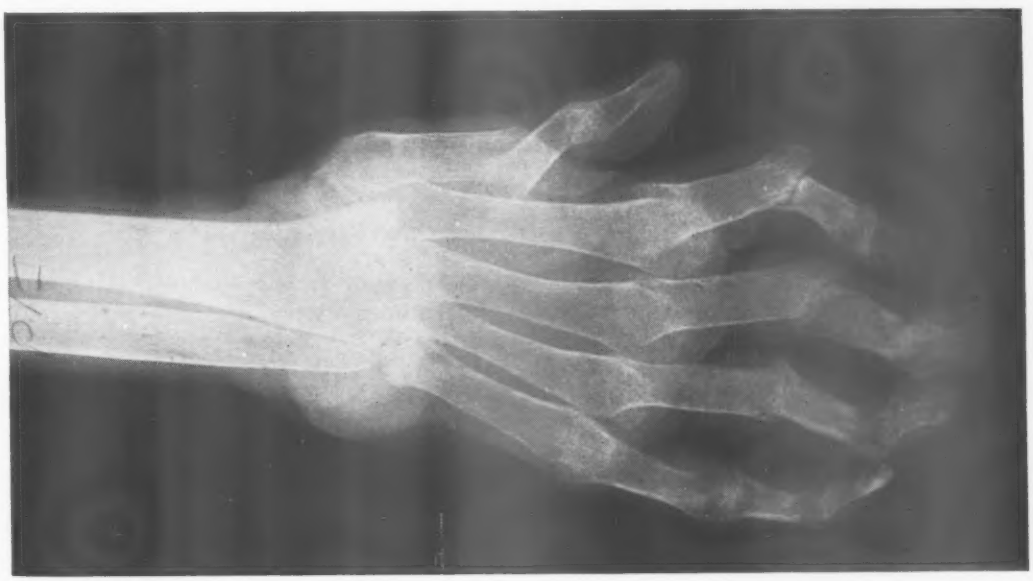


Fig. 6.—*X* ray of the hand of a man with psoriatic arthritis, showing destructive changes of all joints of hand and wrist. Clinically the patient showed *mains en lorgnette.*

been suggested (Wright, 1956b) that some patients with apparently uncomplicated rheumatoid arthritis but a negative differential agglutination test are destined to develop psoriasis. This has since been observed (Dixon, 1958), and strengthens the suggestion that psoriatic arthritis is a distinct entity.

General Manifestations

Radiographically, psoriatic arthritis was less severe than rheumatoid arthritis as evidenced by the diminished frequency of involvement of the proximal interphalangeal joints of the fingers, metacarpo- and metatarso-phalangeal joints, carpus, radio-navicular and radio-ulnar joints, and ulnar styloid process. Generalized osteoporosis was also less marked, particularly in the hands. However, arthritis mutilans with great destruction and melting away of the bones occurred in a few patients. It was of interest that the proximal interphalangeal joints of the toes were more often involved in psoriatic arthritis, in contrast to the analogous joints of the fingers. Asymmetrical involvement, to which attention has previously been drawn (Sherman, 1952), was confirmed radiographically in the metatarso-phalangeal joints.

There was no confirmation of the suggestions that, in patients with psoriatic arthritis when the wrists are involved, there is relative sparing of the metacarpo-phalangeal joints, that the radio-ulnar rather than the radio-navicular joints are involved (Sherman, 1952), or that there is a lack of osteoporosis despite destructive changes (Clemmeson and Arnsø, 1952; Fawcitt, 1950).

Distal Interphalangeal Joints

Characteristic features of psoriatic arthritis included more frequent involvement of the distal interphalangeal joints, especially of the toes. This has been noted by other authors (Benedek, 1955; Golden, 1948; Popp and Addington, 1941; Sherman, 1952). In only one patient were such changes confined to these joints and there seems no justification for restricting the definition of psoriatic arthritis to those patients in whom they are so confined (Bauer, Bennett, and Zeller, 1941). Because of doubt whether to classify the interphalangeal joints of the thumbs as distal or proximal joints they were analysed separately. No significant difference was found between rheumatoid and psoriatic arthritis, but it was noted that in the latter the thumb joints were involved more often than the proximal interphalangeal joints as compared with rheumatoid arthritis.

Erosion of the tips of the terminal phalanges was a characteristic though uncommon feature of psoriatic arthritis, occurring more frequently in the feet. This feature occurred only in relation to nail changes. However, fourteen patients with severe nail involvement but without arthritis did not show such changes. Dense opacities in the terminal phalanges were found among patients with rheumatoid and psoriatic arthritis, and appeared not to be related to the type of arthritis. They were significantly more common in women.

Sacro-Iliac Joints

Frequent mention has been made in the literature of the association of psoriasis and ankylosing spondylitis (Clemmesen and Arnsø, 1952; Dawson and Tyson, 1938; Sterne and Schneider, 1953; Bouwens van der Boijen, 1939; Vilanova and Piñol, 1951), and the term "psoriasis spondylitica" has been coined to describe such cases (Fletcher and Rose, 1955). In the present unselected series, sacro-iliac changes were found more commonly in patients with psoriatic arthritis than in the control group of patients with rheumatoid arthritis, and erosion occurred in 19 per cent. All the psoriatic patients with arthritis mutilans had sacro-iliac joint involvement.

It is interesting to speculate on the relationship of Reiter's syndrome, in which there is a high incidence of sacro-iliac joint disease, to psoriatic arthritis. We have now seen four patients, three of whom are not included in the present series, who in association with non-specific urethritis and arthritis developed keratoderma blennorrhagica which has since progressed to a typical psoriatic picture. In all four the sacro-iliac joints were involved. Histologically it is impossible to differentiate with certainty between pustular psoriasis and keratoderma blennorrhagica. It may well be that there is a link between these two syndromes.

Summary

157 patients with psoriasis and various rheumatic complaints have been studied. In those with osteoarthritis, gout, rheumatic fever, and muscular rheumatism, there were no unusual clinical or radiographic features and their association seemed fortuitous.

121 patients with erosive arthritis were analysed in the light of the Rose-Waaler differential agglutination test and compared with 91 patients with uncomplicated rheumatoid arthritis and a positive test, who were matched by age, sex, and duration of arthritis. In all patients radiographs of the hands, feet, and sacro-iliac joints were taken.

Eighteen patients with psoriasis and erosive arthritis had a positive differential agglutination test and were concluded to be examples of coincidental rheumatoid arthritis on clinical and radiographic grounds. 103 patients with psoriasis, erosive arthritis, and a negative differential agglutination test were thought to be examples of psoriatic arthritis. This arthritis was less severe than rheumatoid arthritis, and was characterized by distal interphalangeal joint involvement, erosion of the terminal phalanges, and a greater incidence of sacro-iliac joint changes.

I am indebted to Prof. S. J. Hartfall and Dr. J. T. Ingram for placing much clinical material at my disposal. Thanks are also due to Dr. A. G. S. Hill, Dr. D. S. Wilkinson, and Dr. R. Spalding Smith, with whom studies on the first patients were done, and to Dr. J. Cowie for invaluable help.

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Étude radiographique comparée de l'arthrite rhumatismale et de l'arthrite associée au psoriasis

RÉSUMÉ

On étudia 157 malades atteints de psoriasis et de diverses affections rhumatismales. Chez ceux atteints d'ostéoarthrite, goutte, rhumatisme articulaire aigu et rhumatisme musculaire il n'y avait pas de traits cliniques ou radiographiques extraordinaires et leur association paraissait fortuite.

A la lumière de la réaction d'agglutination différentielle de Rose-Waaler on analysa 121 cas d'arthrite érosive et on les compara à 91 cas d'arthrite rhumatismale non-compliquée, à réaction positive et aux âges, sexe et durée de l'arthrite assortis. Chez tous les malades on procéda à des radiographies des mains, pieds et des articulations sacro-iliaques.

Dix-huit malades atteints de psoriasis et d'arthrite érosive avaient une réaction d'agglutination différentielle positive et on les considéra, du point de vue clinique et radiologique, comme des exemples d'arthrite rhumatismale coïncidente. Cent trois cas de psoriasis, d'arthrite érosive et de réaction d'agglutination différentielle négative furent considérés comme exemples d'arthrite

psoriasique. Cette arthrite fut moins sévère que la rhumatismale et fut caractérisée par l'implication des articulations inter-phalangiennes distales, l'érosion des phalanges terminales et une plus grande fréquence de lésions articulaires sacro-iliaques.

Estudio radiográfico comparativo de arthritis reumatoide y de arthritis asociada con soriasis

SUMARIO

Se estudiaron 157 enfermos con soriasis y padecimientos reumáticos diversos. En aquellos con osteoartritis, gota, reumatismo poliarticular agudo y reumatismo muscular, no existían rasgos clínicos o radiográficos peculiares y su asociación pareció ser fortuita.

A la luz de la reacción de aglutinación diferencial de Rose-Waaler se analizaron 121 casos de artritis erosiva y se compararon con 91 casos de artritis reumatoide sin complicaciones, con reacción positiva, y con edades, sexo y duración de la artritis correspondientes. En todos los enfermos se tomaron radiografías de las manos, pies y articulaciones sacro-iliacas.

En 18 enfermos con soriasis y artritis erosiva la reacción de aglutinación diferencial era positiva y estos casos fueron considerados, sobre bases clínicas y radiográficas, como ejemplos de artritis reumatoide coincidente. Ciento y tres enfermos con soriasis, artritis erosiva y reacción de aglutinación diferencial negativa fueron considerados como ejemplos de artritis soriásica. Dicha artritis era menos severa que la reumatoide y se caracterizaba por afectar la articulación interfalangiana distal, erosión de las falanges terminales y una mayor incidencia de lesiones articulares sacro-iliacas.

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THE NATURE OF ANAEMIA IN RHEUMATOID ARTHRITIS

V. RED CELL SURVIVAL MEASURED BY RADIOACTIVE CHROMIUM

BY

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A number of studies have been undertaken to assess the importance of shortened red cell survival in the causation of anaemia complicating rheumatoid arthritis. Freireich, Ross, Bayles, Emerson, and Finch (1954), using the Ashby technique, found reduction of the life span of transfused erythrocytes from normal individuals in patients suffering from the disease. Alexander, Richmond, Roy, and Duthie (1956), using the same technique, confirmed this observation in all of eighteen patients, as did McCrea (1957) in ten out of fifteen patients and Freireich, Ross, Bayles, Emerson, and Finch (1957) in "more than half" of thirteen patients. However, Freireich and others (1954, 1957) observed that cells from patients with rheumatoid arthritis survived normally in the circulation of normal individuals; Alexander and others (1956) reported that the survival time of cells from patients with rheumatoid arthritis, although shorter than normal, exceeded that of cells from normal subjects when transfused to other patients with rheumatoid arthritis.

The survival of a patient's own cells in his own circulation cannot be measured by the Ashby technique. Hence it is interesting to review the evidence for a haemolytic process in rheumatoid arthritis that has been obtained with the use of chromium-51 as a red cell label. Bunim (1954) reported the first such study and observed reduction of the survival time of the patients' own cells in all the cases investigated. This was confirmed in a report by Ebaugh, Peterson, Rodnan, and Bunim (1955). Weinstein (1959), also measuring the survival of the patient's own cells in his own circulation, stated that "hyperhaemolysis" contributes to the anaemia of rheumatoid arthritis. However, a study of his data shows that nine of the eighteen patients investigated fell within the normal range of the author's series and that in only four patients (two of whom had splenomegaly) was the rate of disappearance of injected radioactivity clearly increased. Lewis and Porter (1960) used chromium-51 in a study of fifty patients; in only four was survival of the individual's own cells (after correction for elution of chromium) below the normal range, and in these patients the finding appeared to be due to a loss of radioactivity from the circulation, in the first few days of the study, slightly greater than that which is known to occur in normal subjects. These authors, who took care to exclude gastro-intestinal bleeding as a cause of loss of labelled red cells from the circulation, concluded that "haemolysis is not a feature of rheumatoid arthritis and is not a significant factor in the development of the anaemia which is often associated with the disease".

Because of the divergent results of different investigators, it was considered that the following report, which deals with the survival of the subject's own cells and of donor cells from normal individuals in patients with rheumatoid arthritis, would be of interest. The preliminary findings in this investigation have been reported elsewhere (Richmond, 1957).

Methods

21 patients suffering from rheumatoid arthritis were investigated; in each patient the diagnosis of "definite rheumatoid arthritis" had been established by the criteria recommended in the revised classification of the American Rheumatism Association (Ropes, 1959). All were receiving in-patient treatment at the Rheumatic Diseases Unit, Northern General Hospital, Edinburgh.

The patients were unselected; none showed an unusually severe degree of anaemia, clinical evidence of haemolytic disease, or palpable splenic enlargement.

The survival of the patient's own red cells in his own circulation was studied in each case, and in six of the patients the survival of cells freshly withdrawn from compatible healthy donors was also measured.

In five normal individuals the measurement of survival of the subject's cells in his own circulation was used as a standard of normality.

Red cell survival was estimated using the radioactive isotope chromium 51 as a red cell label; the method was that described by Mollison and Veall (1955). Because of the elution of chromium from labelled cells (approximately 1 per cent. per day) it is accepted that the rate of disappearance of injected radioactivity from the patient's circulation can only serve as an index of cell survival. No attempt has been made to correct the results in the present investigation for elution. The first blood sample was withdrawn 1 hour after the injection of chromium-labelled cells and its content of radioactivity constituted the initial level of "100 per cent.". Two further samples of blood were withdrawn in the next 3 days; thereafter samples were obtained twice weekly for at least 20 days.

The methods for determining the peripheral blood counts, the erythrocyte sedimentation rate (E.S.R.), and the agglutination titre of sensitized sheep cells (S.S.C.T.) have been described in previous communications (Richmond, Gardner, Roy, and Duthie, 1956; Bremner, Alexander, and Duthie, 1959).

Results

Clinical and Haematological Status of Patients.—Eleven female and ten male patients were investigated. Clinical and other data on these patients are shown in Table I.

There was a wide range for age, clinical duration of disease, haemoglobin level, erythrocyte sedimentation rate, and agglutination titre for sensitized sheep cells.

Erythrocyte Survival.—As a measure of "cell survival" the linear regression coefficient (*b*) of radioactivity (log. percentage of initial radioactivity) on time (in days) was calculated for the data obtained in each patient. In each case there was a high linear correlation between remaining radioactivity and time (correlation coefficient, $r = -0{\cdot}9361$ to $-0{\cdot}9985$) within the period after injection during which the rate of disappearance was calculated. A plot of the data showed that the relationship was not strictly linear in some cases, but within the chosen limits of 0 to 20 days the linear coefficients were adequate for the purpose of comparing "cell survival" in different individuals and groups.

The following results are summarized in Table II and Fig. 1 (opposite) and Fig. 2 (overleaf).

(*a*) *Own Cells in Normal Subjects.*—The average linear regression coefficient (*b*) for the five normal subjects studied was $-0{\cdot}0107$ ($r = -0{\cdot}9937$). These results are similar to those of Mollison and Veall (1955), for whose data the following figures have been calculated: $b = -0{\cdot}01160$; $r = -0{\cdot}9950$.

TABLE I

CLINICAL AND HAEMATOLOGICAL STATUS OF 21 PATIENTS WITH RHEUMATOID ARTHRITIS, SHOWING RESULTS OF RED CELL SURVIVAL

Case No.	Age (yrs)	Sex	Clinical Duration of Disease (yrs)	Haemoglobin Level per cent. (100 per cent. = 14·8 g./100 ml.)	Erythrocyte Sedimentation Rate (mm./hr)	Sensitized Sheep Cell Test	Linear Regression Coefficient (*b*)*	
							Own Cells	Normal Donor Cells
1	65	F	9	58	82	1:1,024	−0·0131	−0·0148
2		F				1:16	−0·0109	
3	52	M	5	89	48	1:512	−0·0121	
4	46	M	3	63	23	<1:8	−0·0117	−0·0103
5	48	F	9	93	29	1:8	−0·0114	
6	55	M	4	92	80	1:128	−0·0123	
7	56	F	11	63	111	1:16	−0·0092	
8	45	F	3	75	82	1:1,024	−0·0121	
9	33	M	12	82	54	1:1,024	−0·0094	
10	58	F	8	86	55	1:1,024	−0·0126	
11	61	F	1	76	68	1:32	−0·0103	
12	63	F	30	77	80	1:64	−0·0090	
13	50	M	7	57	101	1:32	−0·0101	
14	64	M	2	89	43	1:256	−0·0126	
15	38	M	2	87	55	1:1,024	−0·0104	
16	50	F	8	74	70	1:256	−0·0120	−0·0127
17	51	F	4	96	23	1:16	−0·0113	−0·0122
18	46	M	3	94	38	1:1,024	−0·0115	
19	42	F	9	78	26	1:32	−0·0141	
20	38	M	14	90	34	1:256	−0·0128	−0·0123
21	56	M	1	106	46	1:1,024	−0·0133	−0·0146
Mean	48·4		6·9	77·4	55			

* See text.

TABLE II

ERYTHROCYTE SURVIVAL IN DIFFERENT GROUPS OF SUBJECTS

Group of Subjects	Cells Labelled	Linear* Regression Coefficient (*b*)	Linear* Correlation Coefficient (*r*)
5 Normal Subjects	Own	−0·01070	−0·9937
21 Patients with Rheumatoid Arthritis	Own	−0·01100	−0·9422
6 Patients with Rheumatoid Arthritis in whom Survival of Own Cells and Donor Cells was Studied	Own	−0·01215	−0·9934
	Donor	−0·01302	−0·9578

* See text.

(*b*) *Own Cells in Patients with Rheumatoid Arthritis.*—The average linear regression coefficient (*b*) for the patients with rheumatoid arthritis was −0·01100 ($r = -0·9422$) and comparison of this result with that obtained in normal subjects did not show a significant difference. However, in fifteen of the 21 patients studied, "cell survival" was shorter than the mean for the normal controls.

(*c*) *Normal Cells in Patients with Rheumatoid Arthritis.*—For the six patients (Cases 1, 4, 16, 17, 20, 21) in whom survival of their own cells and those of normal donor cells was measured consecutively, the following results were obtained:

Own cells $b = -0·01215$; $r = -0·9934$;

Normal cells $b = -0·01302$; $r = -0·9578$.

Comparison of the curves for "cell survival" between normal cells in patients with rheumatoid arthritis and own cells in normal subjects showed a difference which was highly significant ($p < 0·001$). Comparison between the curves for normal cells and own cells in patients with rheumatoid arthritis showed no significant difference ($0·1 > p > 0·05$).

There was no apparent relationship between "cell survival", and the age, sex, clinical duration of disease, haemoglobin level, erythrocyte sedimentation rate, and titre in the sensitized sheep cell test.

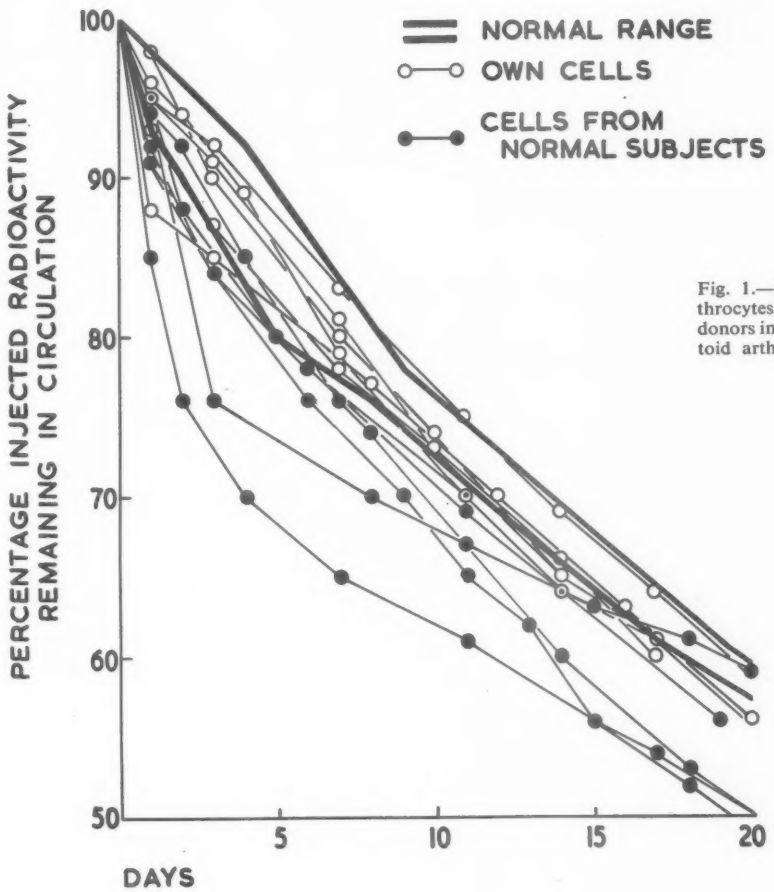

Fig. 1.—Survival of the subject's own erythrocytes and of erythrocytes from healthy donors in six patients suffering from rheumatoid arthritis measured by the radioactive chromium technique.

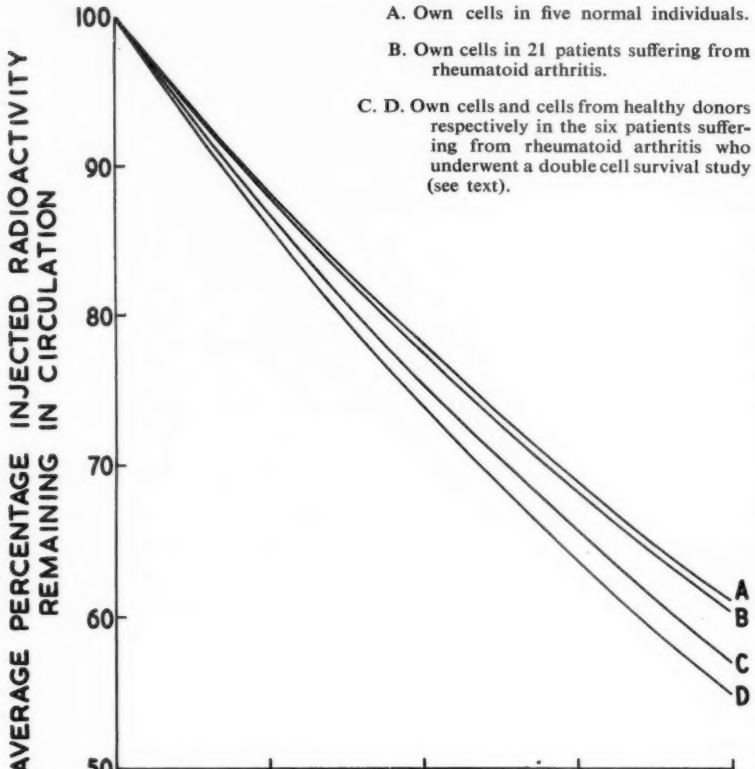

Fig. 2.—Survival of erythrocytes in normal subjects and in patients with rheumatoid arthritis measured by the radioactive chromium technique. The curves have been constructed from the average linear regression coefficient for each group (see text).

Discussion

The majority of investigators who have sought to demonstrate a haemolytic process in patients suffering from rheumatoid arthritis have concluded that reduction of red cell survival has been a factor in the aetiology of anaemia in this condition. The survival curves have indicated random destruction of red cells. The fact that cells from patients with rheumatoid arthritis survive normally when transfused to normal individuals (Freireich and others, 1954, 1957) suggests that the disorder is due to some extracorpuscular factor rather than to an intrinsic abnormality in the erythrocyte.

The largest study was that of Lewis and Porter (1960). These authors, after measuring the survival of the individual's own cells, using the radioactive chromium technique, in fifty patients, reported that in only four instances was there evidence of a slight increase in the rate of red cell destruction. The present investigation confirms this finding; in a proportion of patients with rheumatoid arthritis the injected radioactive chromium disappeared slightly more rapidly than in normal individuals, and while the average curve for "cell survival" was slightly steeper than that for normal subjects, it was not significantly different.

However, when cells from normal donors were transfused into six of the patients with rheumatoid arthritis, the rate of disappearance of injected radioactivity was faster than when the survival of the patients' own cells was measured and significantly faster than in normal subjects.

Mollison (1959) has drawn attention to the misleading results which can arise in cross-transfusion experiments and are presumably due to incompatibility which has not been detected by the usual *in vitro* tests. However, this explanation seems unlikely to obtain in the present investigation. Not only would incompatability be expected to lead to a much greater increase in the rate of red cell destruction than has been observed, but also the finding of accelerated destruction of normal donor cells compared with the patients' own cells confirms our previous results (Alexander and others, 1956) when, because the Ashby technique was used, *all* the studies involved cross-transfusion.

Mollison (1959) suggests that, in a patient with a random destructive process, a sample of the patient's own cells probably contains more young cells and cells that have resisted haemolysis than does a population of cells from a normal individual. Hence more rapid destruction of donor erythrocytes than of the patient's own erythrocytes is characteristic of an extracorpuscular type of haemolytic disorder. This was the finding in the present investigation; in fifteen of the 21 patients with rheumatoid arthritis, "cell survival" was shorter than the average for the normal group, but the transfusion of erythrocytes from healthy donors was necessary before any significant difference could be shown to exist between patients with the disease and normal subjects.

When the present observations are considered, together with the results of previous investigators, it seems likely that there is a mild haemolytic factor

in the causation of the anaemia that is found in patients suffering from rheumatoid arthritis.

Summary

(1) The literature relating to red cell survival in patients suffering from rheumatoid arthritis has been reviewed.

(2) The survival of the subject's own cells has been measured using radioactive chromium in 21 patients suffering from rheumatoid arthritis. In six of these the survival of normal donor erythrocytes was also measured.

(3) The rate of removal of injected radioactivity from the circulation was slightly, but not significantly, more rapid than normal when the patients' cells were labelled. The rate of elimination of labelled donor erythrocytes was significantly faster than normal.

(4) It is concluded that there is a mild haemolytic process of extracorpuscular type in rheumatoid disease.

During the time that this work was being done, the Rheumatic Unit, Northern General Hospital, Edinburgh, was in receipt of grants from the Medical Research Council, the Nuffield Foundation, the Empire Rheumatism Council, and Boots Pure Drug Co.

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Nature de l'anémie dans l'arthrite rhumatismale. V. Survie des globules rouges mesurée par le chrome radioactif

RÉSUMÉ

(1) On passe en revue la littérature concernante la survie des globules rouges des malades atteints d'arthrite rhumatismale.

(2) La survie des érythrocytes propres du sujet fut mesurée à l'aide du chrome radioactif chez 21 malades atteints d'arthrite rhumatismale. Chez six d'entre eux on mesura aussi la survie des globules rouges provenant d'un donneur normal.

(3) Le taux d'élimination de la radioactivité injectée de la circulation fut légèrement mais non pas appréciablement au dessus de la normale en ce qui concerne les globules marqués propres du malade. Le vélocité d'élimination des globules marqués du donneur fut appréciablement augmentée.

(4) On conclut que dans la maladie rhumatismale il existe un benin processus hémolytique du type extracorpusculaire.

Naturaleza de la anemia en la artritis reumatoide. V. Superviviencia de los hematíes medida con cromo radioactivo

SUMARIO

(1) Se pasa en revista la literatura referente a la superviviencia de hematíes de enfermos con artritis reumatoide.

(2) La superviviencia de los eritrocitos propios del sujeto se midió por medio de cromo radioactivo en 21 enfermos con artritis reumatoide. En seis de éstos se midió también la superviviencia de hematíes procedentes de donante normal.

(3) La velocidad de desaparición de la radioactividad inyectada de la circulación fué ligeramente pero no apreciablemente superior a la normal en el caso de eritrocitos propios del paciente. Los eritrocitos marcados de donante sano fueron eliminados con rapidez apreciablemente superior a la normal.

(4) Se concluye que en la enfermedad reumatoide existe un ligero proceso hemolítico del tipo extracorpuscular.

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SARCOIDOSIS PRESENTING WITH POLYARTHRITIS

BY

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Polyarthritis is a frequent presenting symptom in patients with sarcoidosis (Scadding, 1956; James, 1956). It is especially common in association with erythema nodosum; the combination of polyarthritis, erythema nodosum, and bilateral hilar adenopathy forming one of the distinctive syndromes of this disease (Löfgren, 1953; James, Thomson, and Willcox, 1956).

Thus, Löfgren, in his series of 212 cases of bilateral hilar adenopathy believed to be due to sarcoidosis, found 113 cases with erythema nodosum, of whom 101 (89 per cent.) had articular symptoms. Of those without erythema nodosum, eighteen (18 per cent.) had articular symptoms (Löfgren, 1953). Similarly, James (1959) found associated polyarthralgia in 64 per cent. of a series of 62 cases of histologically proven sarcoidosis presenting with erythema nodosum. Despite the marked frequency of polyarthritis in these and other large series, little attention has been given to the pattern or duration of the joint involvement apart from mention of its similarity to acute rheumatism (James, 1958). The striking systemic upset accompanying the polyarthritis has also received little stress.

Löfgren (1953) stated that the articular symptoms are mild in type, generally subsiding within a couple of weeks with reversion to normal of the sedimentation rate; apart from fever at the onset he did not mention systemic symptoms.

This report concerns seven patients seen within a period of 18 months in a general medical unit in all of whom polyarthritis was the presenting symptom. Typical skin changes of erythema nodosum developed subsequently in five cases. The diagnosis of sarcoidosis was confirmed in six cases by the Kveim Test.

Clinical Findings

Age and Sex.—As shown in Table I (opposite), the seven patients consisted of six women and one man, their ages ranging from 28 to 57 years. Six of the patients lived in the country. None of the females had had recent pregnancies. James (1958), working in London, noted that sarcoidosis presenting with erythema nodosum was especially common in women, and mentioned its development coinciding with lactation.

Polyarthritis.—This was the presenting manifestation in all cases, preceding the development of skin lesions (Table I). The average duration of symptoms was 5 weeks (range 2 to 10 wks). In all cases, ultimate resolution occurred without specific therapy and no residual effects have been observed.

Joint involvement was manifested by pain and stiffness, the latter usually being worst in the morning and improving with use. It was chiefly the large joints that were affected (Table II, opposite).

Involvement of the ankle joints, which occurred in six patients, appears to be a striking feature of this form of polyarthritis; the ankles were the first joints involved in five cases and the only joints involved in two. Joint effusions were not present in any case and joint swelling and discoloration were also absent, except in the ankle joints, where marked peri-articular oedema, unrelated to overlying skin changes, was noted in all six cases in which the ankles were affected. The striking incidence of ankle-joint involvement and the presence of peri-articular oedema was noted by Löfgren (1953), but has not been mentioned by workers in Great Britain.

Many workers have stressed the similarity between the polyarthritis in this condition and acute rheumatism. In the present cases, however, the flitting arthralgia of acute rheumatism was never observed, although there was often an interval of 24 to 48 hours between the involvement of successive joints. Furthermore, salicylates had no significant effect on the joint pains in the four cases in which they were given, despite adequate dosage.

In addition to actual arthralgia, four patients complained of marked muscular pain and stiffness, usually in the calves and thighs, but also, in one patient, in the back and shoulders. In two patients, these symptoms preceded the onset of arthralgia by 2 weeks and 3 days respectively, and in the others they developed simultaneously, although they preceded the appearance of skin lesions in all cases.

TABLE I

CLINICAL FINDINGS

Case No	Age (yrs)	Sex	Polyarthritis		Skin Lesions		Systemic Upset	
			Relation to Skin Lesions	Duration (wks)	Nature	Duration (wks)	Nature	Duration (wks)
1	36	M	2 wks before	5	Erythema nodosum	3	Tiredness, anorexia, weight loss, sweating, fever up to 101° F.	5
2	53	F	1 wk before	6	Erythema nodosum	3 "crops" over 5 wks	Tiredness, sweating, generalized aches, fever up to 100° F.	8
3	39	F	10 days before	7	Erythema nodosum	2	Tiredness, sweating, weight loss, generalized aches, fever up to 99·5° F.	9
4	55	F	3 days before	2½	Erythema nodosum	2 Recurrence after 6 wks lasting 1 wk	Tiredness, sweating, weight loss, pains in arms, fever up to 100° F.	18
5	28	F	4 wks before	10	Erythema nodosum	2 "crops" over 4 wks	Tiredness, sweating, anorexia, weight loss, diffuse pains, no fever	11
6	57	F	No skin lesions	2	None		Tiredness, sweating, fever up to 99° F.	12
7	43	F	1 wk before	3	Erythema multiforme	1	Tiredness, anorexia, weight loss, no fever	3

TABLE II

INCIDENCE OF JOINT INVOLVEMENT

Joints Involved	No. of Cases
Ankles	6
Knees	4
Hips	1
Hands	3
Wrists	3
Elbows	3
Shoulders	2

Skin Lesions.—Erythema nodosum developed in five patients. The lesions, which were typical in appearance, were always present on the legs, but also occurred on the arms in two cases. In three cases, successive "crops" of lesions appeared, two having two "crops" and one three "crops". There was no apparent relationship in these patients between joint symptoms and the "crops" of skin lesions. In one other patient, erythema multiforme developed, and the last showed no skin lesions at all. The duration of the skin lesions and their relationship in time of onset to the joint symptoms is shown in Table I. Transient papular or vesicular rashes, as described by James (1959) in this type of case, were not seen.

Systemic Symptoms.—These were present in every case, with accompanying persistent fever in five cases. The relevant symptoms and their duration are shown in Table I.

In four cases, the development of systemic symptoms coincided with the onset of joint symptoms, but in three cases, they preceded the onset of joint symptoms by several weeks. In the majority of cases, the two groups of symptoms subsided simultaneously.

Two patients gave a history of sore throat, but this followed the onset of arthralgia in both instances, although it preceded the appearance of erythema nodosum by 2 and 3 days respectively. Sulphonamides had not been given in either case.

Superficial lymph-gland enlargement and hepatosplenomegaly were never found and examination of the eyes and other systems failed to reveal evidence of sarcoidosis. None of the patients had clinical evidence of cardiac involvement.

Electrocardiograms were taken in four cases and two showed non-specific myocardial changes, maximal in the left ventricular leads. The time of persistence of these changes is unknown, but both had reverted to normal 3 months later. Similar transient electrocardiographic changes were noted by Löfgren (1953) in ten of 69 cases of sarcoidosis presenting with hilar adenopathy.

Radiographic Findings

Only one patient (Case 7) has maintained a normal chest *x* ray throughout the period of obser-

vation. Bilateral hilar lymph-gland enlargement is the typical initial finding in this type of case and was noted in five cases (Fig. 1*a*) with associated enlargement of the right paratracheal glands in three. One patient (Case 6) initially showed unilateral glandular enlargement, but this later became bilateral. This is a rare mode of presentation and this case has been reported in greater detail elsewhere (Williams, 1961). With the exception of this case, the hilar lymph-gland enlargement has always been maximal when the patients were first seen, slow resolution thereafter occurring.

In two patients (Cases 1 and 2), complete clearing occurred within one year without other changes developing (Fig. 1*b*), and in one patient (Case 5) followed for 4 months gradual resolution is occurring.

In three patients (Cases 3, 4, and 6), pulmonary infiltration developed between 4 and 6 months after the onset whilst the hilar lymph glands were resolving (Fig. 2*a*, *b*, opposite) and has persisted unchanged over a period of observation of 6 months.

X rays of involved joints in four cases showed no abnormalities.

Other Investigations

Erythrocyte Sedimentation Rate (E.S.R.).—This was always raised and, with one exception, the initial readings were greater than 40 mm./hr (Westergren) (Table III). In this one patient (Case 2), the initial reading was 24 mm./hr and this had fallen to normal within 2 weeks. The elevation persisted for several months in the other patients and in one (Case 6) is still elevated at 40 mm./hr, 9 months after the onset.

TABLE III

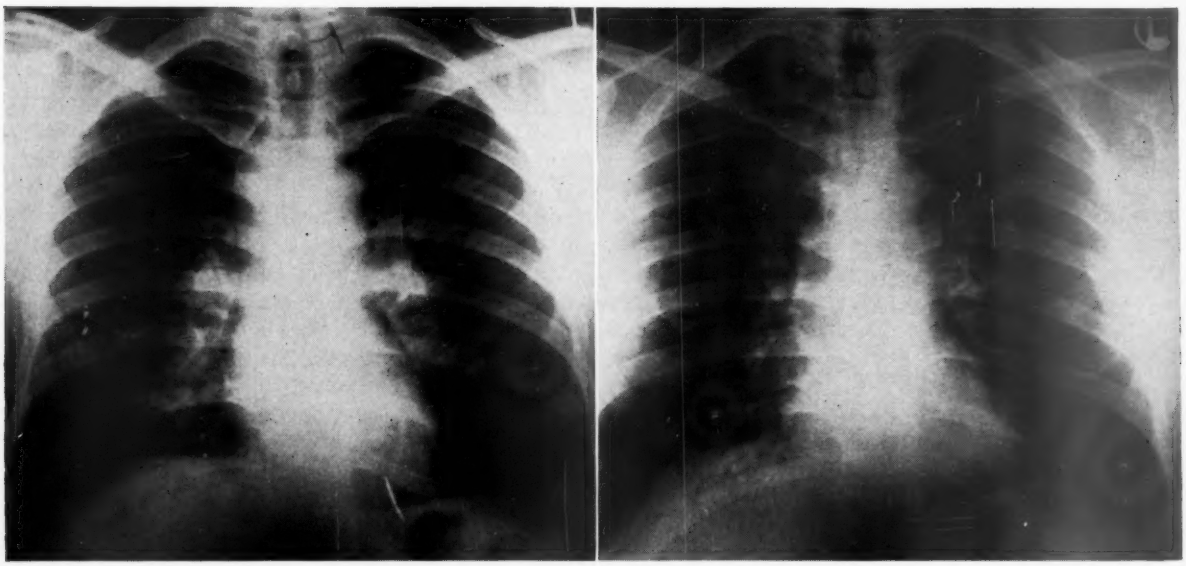
INITIAL ERYTHROCYTE SEDIMENTATION RATE (mm./hr Westergren) AND DURATION OF ELEVATION

Case No.	Initial Reading	Duration of Elevation (mths)
1	40	4
2	24	0·5
3	108	4
4	100	5
5	48	3
6	70	9*
7	70	5

Intradermal Reaction.—The reaction to old tuberculin was tested in all patients. Four cases showed no reaction at 1:100 and one no reaction at 1:1,000, greater dilutions not being used. Two cases gave positive reactions at 1:1,000.

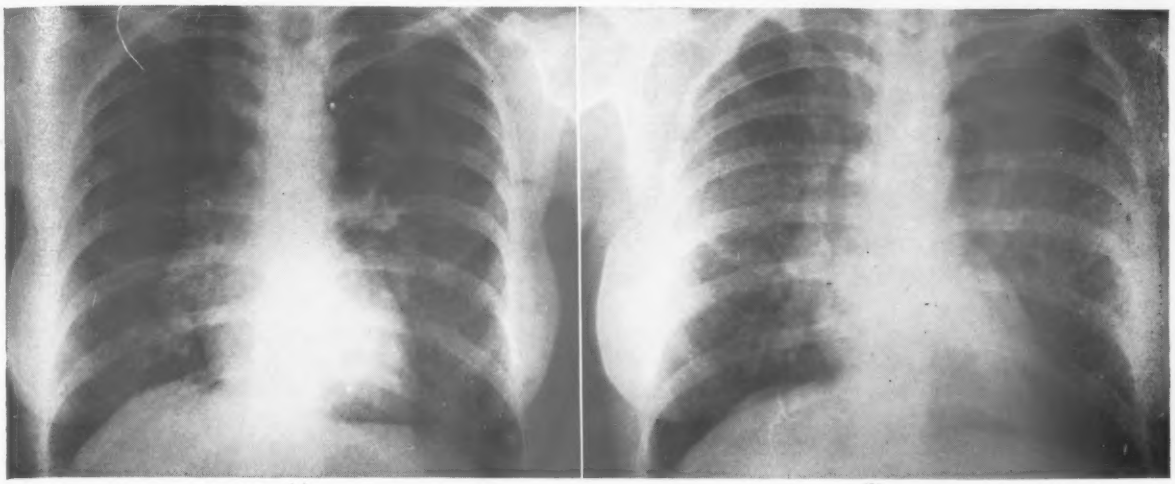
Rose-Waaler Test.—This was negative in all cases and the antistreptolysin titre was always normal. This latter test is useful in distinguishing cases of erythema nodosum due to sarcoidosis from cases due to streptococcal infection.

Estimation of serum proteins showed some elevation of the globulin fraction in all cases.



(*a*) (*b*)

Fig. 1.—Case 1, chest *x* ray.
(*a*) March, 1959, bilateral hilar lymph-gland enlargement, and enlargement of right paratracheal glands.
(*b*) April, 1960, glandular enlargement resolved, and lung fields clear.



(*a*) (*b*)

Fig. 2.—Case 3, chest *x* ray.
(*a*) December, 1959, bilateral hilar lymph-gland enlargement, and lung fields clear.
(*b*) September, 1960, slight resolution of hilar lymph-glands, and marked pulmonary infiltration.

Electrophoretic analysis showed this to be due to increase in the alpha-2 and gamma fractions, especially the latter.

Kveim Test.—Histological evidence of sarcoid tissue is necessary to establish a diagnosis of sarcoidosis. The Kveim test is eminently suitable in the present type of case where there were no superficial lymph-glands or suitable skin lesions available for biopsy. This test was performed in all seven patients, a sarcoid antigen of known potency being used. Positive results were obtained in six patients, an indolent nodule developing at the site of the injection. This was biopsied 4 weeks after injection and histological evidence of sarcoid tissue was found in all six cases (Fig. 3).

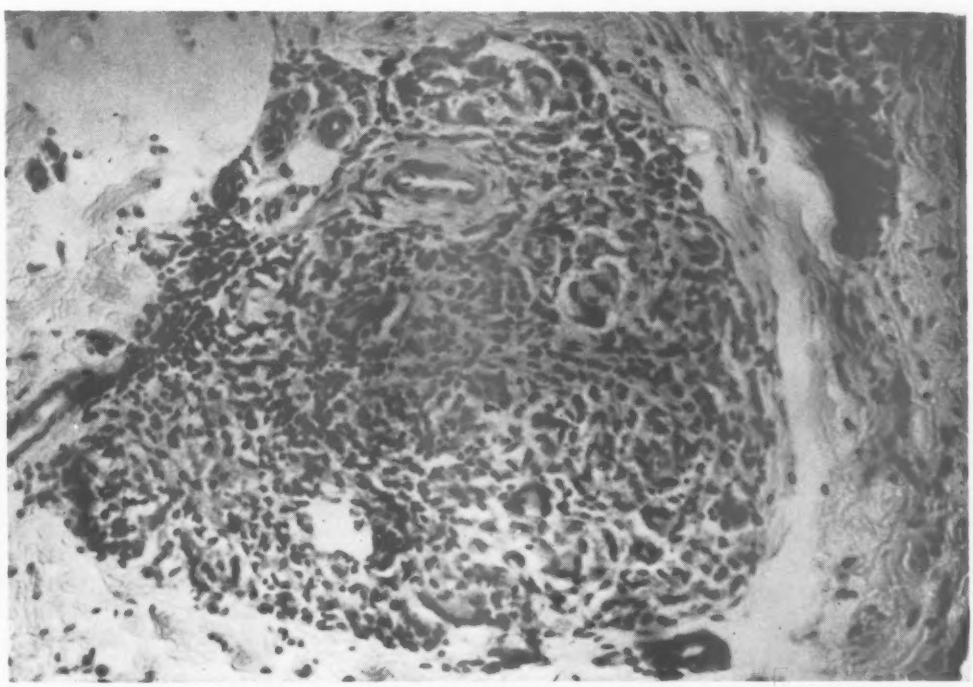


Fig. 3.—Case 3, biopsy of Kveim test, showing typical positive result. Infiltration of dermis with epitheloid cells, lymphocytes, and giant cells. No necrosis or caseation. Haematoxylin and eosin ×480.

In the one case in this series giving a negative test, prednisone had been given during the "latent" period and this is known to influence the response (James and Thomson, 1959).

Treatment

Since the polyarthritis, skin lesions, and systemic upset ultimately settle spontaneously, specific treatment is rarely necessary for these features. Salicylates were given to four of the present patients without apparent effect. Prednisone was given to two patients (Cases 1 and 6) with persistent systemic upset and fever, with rapid response; both were given prednisone in an initial dose of 20 mg. daily, the dose being "tapered off" after 4 weeks. As expected, this had no beneficial effect on the course of the radiological changes and no apparent effect on the erythrocyte sedimentation rate. It is now suggested that these drugs are better avoided at this stage of the disease in view of the theoretical risk of their interfering with immune mechanisms (James, 1959).

Discussion

Polyarthritis was the feature common to all the cases in this series and the joint symptoms conformed to a fairly distinctive pattern. It was chiefly the large joints which were affected with a high incidence of involvement of the ankle joints. Pain and stiffness resulted, but joint swelling was not seen, although periarticular oedema of the ankles was common. These symptoms were usually accompanied by fever, general systemic upset, and striking elevation of the erythrocyte sedimentation rate. In a large proportion of cases, erythema nodosum and hilar adenopathy also occurred, the combination of polyarthritis, erythema nodosum, hilar adenopathy, and systemic upset constituting the fully-developed syndrome.

The course appears to be benign, the joint symptoms and systemic upset subsiding spontaneously after a few weeks and the E.S.R. after several months. The prognosis with regard to the pulmonary lesions in sarcoidosis presenting with these features also appears to be good (James and others, 1956; Scadding, 1956).

Hilar adenopathy is believed to represent the onset phase of pulmonary sarcoidosis (Löfgren, 1953), but the precise cause of the associated skin and joint lesions is uncertain. It is generally believed that erythema nodosum represents a non-specific allergic reaction (Scott, 1956), and the polyarthritis and systemic symptoms may have a similar causation. This would readily explain the occurrence of these features with erythema nodosum irrespective of its aetiology (Scott, 1956). In sarcoidosis presenting with this syndrome, however, sarcoid tissue has been found on biopsy of striated muscle (Myers, Gottlieb, Mattman, Eckley, and Chason, 1952) and on biopsy of the nodal skin lesions (James and others, 1956). This suggests that actual tissue involvement may be responsible for many of the symptoms rather than a non-specific reaction. In only one reported case has synovial biopsy been performed in the acute phase in this syndrome, and this showed only a mild infiltration of mononuclear cells around blood vessels and in the synovial tissue (Ferguson and Paris, 1958).

When polyarthritis, erythema nodosum, hilar adenopathy, and systemic symptoms occur together, the diagnosis of sarcoidosis presents little difficulty, but in incomplete forms (such as Case 7 in this series) diagnosis is more difficult. In cases with associated erythema nodosum the absence of a history of preceding sore throat and a normal antistreptolysin titre are valuable in excluding preceding streptococcal infection, whilst drug sensitivity and primary tuberculous infection will also have to be considered. In doubtful cases the Kveim test appears to provide a fairly reliable diagnostic procedure, positive results being expected in about 80 per cent. of cases (Siltzbach and Ehrlich, 1954; James and others, 1956). Early diagnosis is important, so that, with knowledge of the good prognosis, unnecessary hospitalization and treatment may be avoided.

In view of the good prognosis it is probably advisable to avoid the use of cortisone or its analogues in the early phases of this condition (James, 1959), and to restrict their use to cases in which persistent pulmonary infiltration develops (James, 1956).

Summary

Seven patients with sarcoidosis are reported, all of whom presented with polyarthritis. The clinical features are reviewed with particular emphasis on the pattern of joint involvement and its duration. Fever and systemic symptoms persisting for several weeks accompanied the polyarthritis and the erythrocyte sedimentation rate was usually elevated for several months. Erythema nodosum was present in five patients and pulmonary changes in six. Attention is drawn to the value of the Kveim test in diagnosis. In all cases, symptoms subsided spontaneously in several weeks and specific treatment appeared to be unnecessary. The possible cause of the various symptoms is discussed.

I should like to thank Dr. Ian Gordon for advice during the preparation of the paper and for permission

to report these cases, all of whom were admitted under his care. I should also like to thank Dr. A. W. Branwood for the histological interpretation of the Kveim tests and Mr. A. Topp for the photographs.

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Sarcoïdose débutant par une polyarthrite

RÉSUMÉ

On rapporte sept cas de sarcoïdose débutant tous par une polyarthrite. On passe en revue les traits pathologiques, avec mention spéciale de l'implication articulaire et de sa durée. Une fièvre et des symptômes généraux accompagnaient la polyarthrite pendant plusieurs semaines et la vélocité de sédimentation érythrocytaire était habituellement élevée pendant plusieurs mois. L'érythème noueux était présent chez cinq malades et des lésions pulmonaires chez six d'entre eux. On attire l'attention à la valeur diagnostique de la réaction de Kveim. Dans tous les cas, les symptômes se sont abattus spontanément en quelques semaines et aucun traitement spécifique n'avait semblé nécessaire. On discute la cause possible de différents symptômes.

Sarcoidosis presentándose con poliartritis

SUMARIO

Se presentan siete enfermos con sarcoidosis, todos ellos manifestando poliartritis. Se revisan los rasgos patológicos, con especial mención del tipo de afectación articular y su duración. La poliartritis iba acompañada de fiebre y sintomatología general que persistió durante varias semanas y la velocidad de sedimentación eritrocitaria alta se mantuvo por varios meses. Cinco enfermos presentaron eritema nudoso y en seis se vieron alteraciones pulmonales. Se llama atención hacia el valor diagnóstico de la reacción de Kveim. En todos los casos los síntomas regresaron espontáneamente en varias semanas y el tratamineto específico fué innecesario. Se discute la posible causa de varios síntomas.

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EFFECTS OF ENVIRONMENTAL TEMPERATURE UPON CAPILLARY RESISTANCE IN PATIENTS WITH RHEUMATOID ARTHRITIS AND OTHER INDIVIDUALS

BY

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In two previous surveys of capillary resistance (C.R.) it was found that the mean resistance in groups of patients with rheumatoid arthritis was significantly lower than in groups with other diseases (Potter and Wigzell, 1957). In these surveys the inter-subject variation of C.R. was substantial, even after allowance was made for the systematic influence of age, sex, and disease. The data consisted of the results of one test per individual and therefore provided no information on the nature of the residual variation. This presumably included genuine inter- and intra-subject variation, together with variation due to experimental error. As with other methods for measuring C.R., the negative pressure tests used in these surveys cannot be repeated in a given area of skin at intervals of less than 24 hours, hence strict replication is impossible, and the error of the test cannot be measured directly.

In a retrospective analysis of existing data it is permissible to deduct a proportion of the total variation which can be assigned to the systematic influence of any factor, such as correlation with the ages of the subjects tested, provided that there is a precedent or other independent evidence for the correlation.

With regard to the second of the foregoing surveys, analysis of the data revealed a statistically significant inverse relationship between the results of C.R. tests and environmental temperature, but only in the group of patients with rheumatoid arthritis. Since it lacked the support of independent evidence, this finding was omitted from the original report pending confirmation.

There is evidence that tests of capillary resistance may be a measure of some property of connective tissue (Potter and Wigzell, 1957), and it was concluded that the possible relationship between C.R. and environmental temperature merited further investigation. While it is a popular belief that weather has a determining influence upon rheumatic symptomatology, such experience is neither universally nor consistently described by those suffering from musculo-skeletal disorders.

In planning the experiments reported here, it was decided that a minimum of five C.R. tests at 1- or 2-day intervals would serve as a basis for exploring the effects of environmental temperature in a suitable number of patients. It was further considered that precise quantitation of a relationship between C.R. and environmental temperature should not be expected, since both measurables were likely to have a large experimental error. However, it was believed that any real trend would be demonstrable by this approach, which has indeed confirmed that there is an inverse relationship between C.R. in patients with rheumatoid arthritis and environmental temperature.

Material and Methods

A total of 900 C.R. tests were performed in 72 subjects, including four normal individuals, 41 patients with rheumatoid arthritis, and 27 patients with other diseases (Table I).

TABLE I

COMPOSITION OF GROUPS INVESTIGATED

Group (by diseases)	Number Investigated			Age (yrs)		
	Male	Female	Total	Max.	Min.	Mean
Rheumatoid Arthritis	24	17	41	67	17	51
Other Diseases ..	13	14	27	76	20	43
Normal	3	1	4	45	28	35
Rheumatoid Arthritis during Administration of Steroid* ..	(15)	(9)	(24)	67	18	48
Total	40	32	72			

* Cortisone orally 50-100 mg. per 24 hrs, or Prednisolone orally 5-20 mg. per 24 hrs

The diagnosis of rheumatoid arthritis was in accordance with the criteria for "definite R.A." proposed by the American Rheumatism Association (Ropes, Bennett, Cobb, Jacox, and Jessar, 1957). While under investigation, each patient was confined to bed within the ward for the whole or greater part of the day. The majority of tests were performed during the forenoon. Treatment of the patients with rheumatoid arthritis was maintained during the investigation. It consisted of supportive and corrective physical therapy, together with the administration of analgesics, mainly salicylates.

Additional C.R. tests were performed in 24 of the patients with rheumatoid arthritis during periods in which they received oral cortisone or prednisolone for therapeutic or investigative purposes. It has been shown that cortisone and ACTH have a profound effect upon C.R. in rheumatoid arthritis (Robson and Duthie, 1952) and, for this reason, the data obtained on C.R. in patients receiving steroid hormones were excluded from the general analysis of variance.

The atmospheric temperature was recorded after each C.R. test from a mercury thermometer placed near the subject. In some experiments these data were supplemented by continuous records of atmospheric temperature obtained with a thermograph situated near the patient or patients under observation. To test the possibility that C.R. might be influenced by other environmental factors indirectly measured by the atmospheric temperature in the ward, additional data were obtained from the records of a nearby meteorological station.

The negative pressure apparatus, consisting of a suction pump, reservoir, manometer, control valves, and a 23-mm. suction cup, has been described previously (Potter and Wigzell, 1957). In each test, the cup was used to transmit a series of negative pressures, of −50, −100, −150, ... mm. Hg, all to the same area of skin. Each negative pressure was maintained for 30 seconds, and the petechiae, if any, were counted in the following interval of 30 seconds when the cup was lifted from the skin. The procedure was terminated when ten or more petechiae were produced within the skin under the cup.

The "critical petechial pressure" has been defined as the negative pressure producing only one petechia in a given area of skin exposed for a specified interval (Robson and Duthie, 1950). From extended observation it has become apparent that the numbers of petechiae increase in a logarithmic fashion in response to pressures more negative than the "critical pressure". In other words, there exists a close linear correlation between *log. no. of petechiae* and *applied negative pressure in mm. Hg*. On this basis it was possible to determine the regression equation most closely fitting the successive counts of petechiae in a C.R. test, and from this equation to estimate the negative pressure eliciting exactly ten petechiae. The result of each test was recorded as the figure so obtained, and provided a simple index of resistance which minimized the effect of random errors in the original petechial counts. In practice the index was read from a Table incorporating the appropriate function for three to five petechial counts at 50-mm. increments of negative pressure.

All tests were performed on the area of skin located by aligning the outer rim of the suction cup with the biceps tendon and with the lowermost crease at the elbow.

Results

As this investigation was designed to explore possible relationships between environmental temperature and capillary resistance, correlation between these two variables was estimated for each subject individually (Table II).

TABLE II

DISTRIBUTION OF POSITIVE AND NEGATIVE COEFFICIENTS OF CORRELATION OR OF REGRESSION OF C.R. ON ATMOSPHERIC TEMPERATURE

Group (by disease)	Sex	No. of Individuals in whom Coefficients were		Total
		Positive	Negative	
Patients with Rheumatoid Arthritis (untreated)	Male ..	3	21	24
	Female ..	4	13	17
	Total ..	7	34	41
Patients with Other Diseases and Normal Subjects	Male ..	9	7	16
	Female ..	11	4	15
	Total ..	20	11	31
Patients with Rheumatoid Arthritis (on steroids)	Male ..	9	6	15
	Female ..	7	2	9
	Total ..	16	8	24

For distribution of positive and negative coefficients between patients with rheumatoid arthritis and unaffected patients, $X^2 = 15$; $P < 0{\cdot}01$.

For distribution of positive and negative coefficients in patients with rheumatoid arthritis (untreated) and in patients with rheumatoid arthritis on steroids, $X^2 = 15$; $P < 0{\cdot}01$.

Although only 21 per cent. of the coefficients are significant at a probability of 1 in 20, the distribution of positive and negative coefficients is significantly non-homogeneous.*

On this basis, the estimated error deviation of capillary resistance was 46 mm. Hg (Table III, overleaf).

This value is proportionately little greater than the error of many other biological measurables. The significant differences in C.R. between individuals within each group support the view that the observed variation in resistance occurs around a level characteristic for each individual.

Six patients with rheumatoid arthritis were

* If no real correlation existed, the estimated coefficients should be distributed symmetrically around zero, and in any large sample the number of "significant" coefficients (at a probability of 1 in 20) should approach 5 per cent.

TABLE III

ANALYSIS OF VARIANCE IN 900 C.R. TESTS IN 72 INDIVIDUALS

Source of Variation	Sum of Squares		Degrees of Freedom		Mean Square		Variance Ratio
Between Groups*		246,633		3		82,216	13·3†
Within Groups*		5,548,035		896		6,192	
Between Individuals	3,640,595		69		52,762		24·5†
Within Individuals —With Environmental Temperature	281,633		71		3,967		1·8†
—Residual	1,626 307		756		2,151		
Total		5,794,668		899			

* Four Groups: Patients with Rheumatoid Arthritis —Male
—Female
Other Subjects —Male
—Female

† Significant at the 1 per cent. level.

exposed to large fluctuations of environmental temperature over a period of one week, during which the C.R. was measured twice daily on alternate arms. In these circumstances it was readily apparent that resistance varied inversely with atmospheric temperature (Figure).

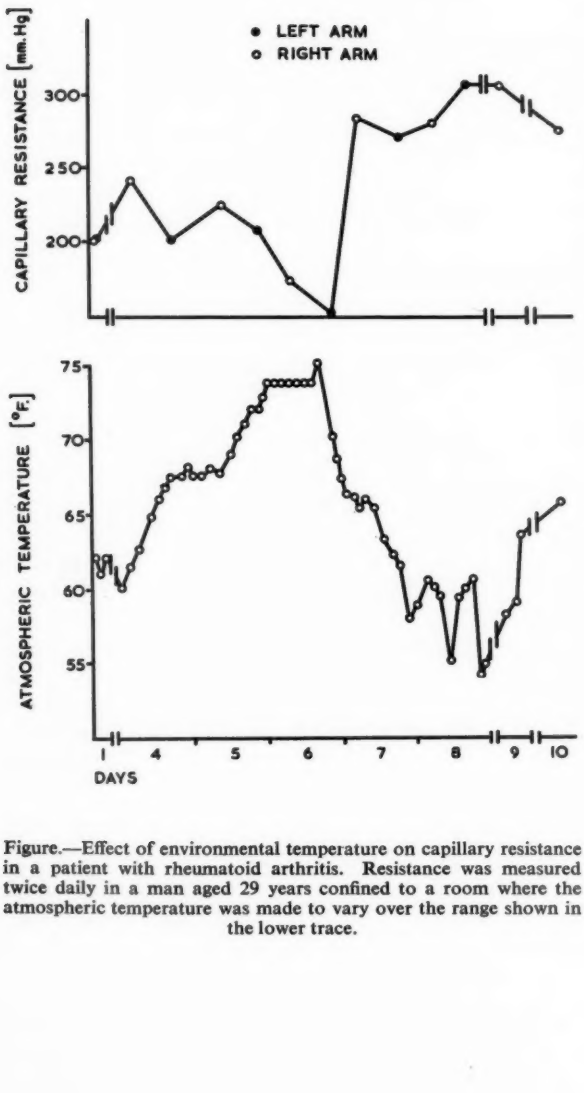

Figure.—Effect of environmental temperature on capillary resistance in a patient with rheumatoid arthritis. Resistance was measured twice daily in a man aged 29 years confined to a room where the atmospheric temperature was made to vary over the range shown in the lower trace.

However, it was evident that the resistance might be influenced more by the direction of temperature change than by the actual level of temperature; *i.e.* in response to a rise in temperature the C.R. fell initially, but subsequently increased again if the temperature was maintained at the new level.

From all of the data it has been estimated that, in patients with rheumatoid arthritis, the C.R. tended to vary inversely with environmental temperature. (On average, resistance fell by 4 mm. Hg with a temperature increase of 1° F., and *vice versa.*) In other subjects the resistance tended to vary directly with environmental temperature. (On average, resistance increased by 2 mm. Hg with a temperature increase of 1° F., and *vice versa.*) The data on C.R. in patients receiving cortisone or prednisolone were analysed separately and the results are outlined in Table II. In patients with rheumatoid arthritis a negative correlation between C.R. and temperature was no longer apparent during steroid therapy. Instead, the resistance tended to vary directly with the temperature, but the average correlation was not significant. This effect of steroids will be discussed.

Appropriate tests showed some correlation between the temperature of the atmosphere within the wards (measured with a mercury thermometer or thermograph) and the external temperature recorded at the meteorological station. This may be a measure of the efficiency of the central heating system and probably also reflects a traditional regard for the therapeutic value of fresh air, however cold. The pattern of correlation between C.R. and temperature was essentially the same for all sources of data on the latter; there was no correlation between capillary resistance and barometric pressure.

Discussion

From the foregoing data it has been inferred that in 72 subjects a significant proportion of the vari-

ability of capillary resistance was a consequence of fluctuation in the atmospheric environmental temperature. In this group, furthermore, the patients with rheumatoid arthritis differed from the other individuals in the pattern of the C.R. response to a change of environmental temperature. The biological mechanisms involved in the response are as yet unidentified, but the results indicate that experimental error alone does not explain the rise or fall of resistance occurring in an individual within the 24-hour period between successive determinations.

The variability of C.R. thus demonstrable implies a similar lability in the tensile strength of tissues supporting the small cutaneous blood vessels. In terms of histology, the perivascular "sheath" of connective tissue shows little or no variation except when it has been disorganized, for example, by a relatively gross focal inflammatory lesion, and for this reason might be regarded as having little or no dynamic potential. In contrast, the cutaneous vessels *per se* are highly responsive to neurohumoural stimuli. While it might be reasonable to assume that the day-to-day variability of C.R. is a manifestation of changes in vasomotor activity, there is impressive evidence to the contrary. In a series of careful experiments performed on normal subjects, Wigzell (1958) found that capillary resistance was essentially uninfluenced by reflexly-induced vasodilatation and constriction, despite a well-marked vasomotor response throughout the area of skin where the C.R. was determined. From evidence previously reviewed, moreover, it was concluded that capillary resistance is a measure of some property of the connective tissue ensheathing small cutaneous vessels and particularly the collecting venules (Peck, Rosenthal, and Erf, 1937; Zweifach, 1955; Potter and Wigzell, 1957; Wigzell, 1958).

The perivascular sheath can be considered to include two major components forming a network of collagen fibres in a matrix of amorphous ground substance. Of the two components, the second would seem to have the greater potential for undergoing rapid changes of state. It is conceivable that a change in the properties of ground substance could modify the tensile strength of the collagen network, and yet escape detection by existing histological techniques. Analogous interdependence of structural components is evident in other tissues such as bone and, probably, articular cartilage (McElligott and Potter, 1960).

In the course of the investigation it was observed that administration of corticosteroid hormones to patients with rheumatoid arthritis modified the effect upon the C.R. of a change in the environmental temperature. During steroid administration correlation between resistance and temperature was in general less negative than in untreated patients and thus tended to approach the positive direct correlation which was characteristic both of the group of patients with diseases other than rheumatoid arthritis and of the group of normal individuals. This effect need not signify that steroid administration corrected any defect fundamental to the "abnormal" pattern of C.R. response in patients with rheumatoid arthritis, but in the context of this discussion it is relevant to postulate that the hormonal effect was mediated by changes occurring primarily in the perivascular connective tissue, or else in the mechanism linking this tissue with the environment. While the latter possibility is entirely speculative, there is some evidence that cortisone has a local effect upon the amorphous component of dermal connective tissue, since restoration of the "dermal barrier" after injection of hyaluronidase was accelerated in patients with Still's disease during treatment with cortisone (Bywaters, Holborow, and Keech, 1951).

At present little is known about the true nature of the properties measured indirectly by negative pressure C.R. tests. Hence it is necessary to defer complete evaluation of the biological significance of the effects of environmental temperature described in this report. That individuals differ in their response to environmental temperature may be of practical importance in surveys to determine C.R. in health and disease. Such data, reported by a number of different observers, have appeared in some instances to be mutually contradictory (Hare and Miller, 1951). These anomalies might well have arisen from the unrecognized influence of the subjects' environmental temperature in the interval before a C.R. test performed under standard environmental circumstances.

Finally, the present findings may be regarded as objective evidence of a relationship between "rheumatism" and "weather". Obscure and complex as it appears to be, such a relationship has escaped demonstration in any previous multifactorial exploration.

Summary

(1) Capillary resistance (C.R.) was measured repeatedly in individual subjects, including 41 patients with rheumatoid arthritis and 27 with other diseases.

(2) Analysis of the results revealed a negative correlation between C.R. and environmental temperature in the group of patients with rheumatoid

arthritis. In contrast, correlation between the two variables was positive in the remaining group of subjects.

(3) During administration of corticosteroid hormones to patients with rheumatoid arthritis, the correlation between C.R. and temperature tended to become more positive, *i.e.* less "abnormal".

(4) These findings are discussed in terms of their implications in relation to the structure and function of the tissues supporting the small cutaneous blood vessels.

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Effet de la température ambiante sur la résistance capillaire chez des malades atteints d'arthrite rhumatismale et chez d'autres sujets

RÉSUMÉ

(1) On mesura à plusieurs reprises la résistance capillaire chez un nombre de sujets, y compris 41 malades atteints d'arthrite rhumatismale et 27 sujets atteints d'autres maladies.

(2) L'analyse des résultats montre une corrélation négative entre la résistance capillaire et la température ambiante dans le groupe des malades atteints d'arthrite rhumatismale. Par contre, la corrélation entre les deux variables fut positive chez tous les autres.

(3) Pendant l'administration d'hormones corticostéroïdes aux malades atteints d'arthrite rhumatismale, la corrélation entre la résistance capillaire et la température ambiante tendait à devenir positive, c'est-à-dire, moins "anormale".

(4) On discute ces résultats du point de vue de leurs implications en ce qui concerne la structure et la fonction des tissus qui supportent les petits vaisseaux sanguins de la peau.

Efecto de la temperatura ambiente sobre la resistencia capilar en enfermos con artritis reumatoide y en otros sujetos

SUMARIO

(1) Se midió repetidamente la resistencia capilar en un grupo de sujetos que comprendía también 41 enfermos con artritis reumatoide y 27 con otras enfermedades.

(2) El análisis de los resultados demuestra una correlación negativa entre la resistencia capilar y la temperatura ambiente en el grupo de enfermos con artritis reumatoide. En contraste, la correlación entre las dos variables fué positiva en el resto de los sujetos.

(3) Durante la administración de hormonas corticosteroides a enfermos con artritis reumatoide la correlación entre la resistencia capilar y la temperatura ambiente tendía a ser positiva, esto es, menos "anormal".

(4) Se discuten tales hallazgos desde el punto de vista de sus implicaciones en relación con la estructura y función de los tejidos que contienen los pequeños vasos cutáneos.

Ann. Rheum. Dis. (1961), **20**, 149.

RHEUMATIC COMPLAINTS IN A RURAL POPULATION

BY

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The geographic distribution of disease is a subject in which increasing interest has been shown in recent years. Cobb and Lawrence (1957) summarized the findings in nine surveys of the prevalence of rheumatoid arthritis in different countries and discussed some of the factors which might contribute to the varying results reported. The prevalence of rheumatic complaints other than rheumatoid arthritis has received less attention. Kellgren, Lawrence, and Aitken-Swan (1953), in a study of rheumatic complaints in Leigh in Lancashire, included accounts of the prevalence of osteo-arthrosis, disk lesions, and other conditions. De Blécourt (1954) included osteo-arthrosis, ankylosing spondylitis, and "rheumatism of the soft tissues" in his report from Holland.

The present study was undertaken to investigate the prevalence of rheumatic complaints in an isolated rural community in England, in which the majority of the population were born in the district and had lived and worked there all their lives, and amongst whose ancestors there had been much inter-marriage. It was thought that such a study might offer a useful comparison with others of populations with different genetic, environmental, and occupational backgrounds.

This paper reports the prevalence of rheumatic complaints in two groups of people, those born in the district and those coming into it from other parts of the country, and discusses some features of inflammatory polyarthritis found in these groups.

The District and the People

Wensleydale is in the North Riding of Yorkshire. The valley runs from West to East and at its upper end is about 850 ft. above sea level, the fells rising steeply to over 2,000 ft. on either side. The rock formation is sandstone and shale, with bands of limestone. The soil is glacial lake silts and boulder clay, with peat on the fell tops, above millstone grit. The land in the valley is rough pasture and the only crop is hay. The sea is 25 miles distant at its nearest point and the nearest towns are 30 to 40 miles away.

The area is close to the Pennine watershed and is subject to violent rainstorms. There is usually heavy snow at some time during the winter. The mean monthly rainfall varies from 5·42 in. at the head of the Dale, to 3·72 in. at Bainbridge, 10 miles down the valley (range 0·33-11·13). The mean monthly sunshine figure is 101·3 hrs (range 14·5-251·5). The mean maximum and minimum temperatures are 75° F. and 18° F. (mean 44·1° F.).

The water is hard, with temporary and total hardness of 140 parts/million and a pH of 7·3.

The area chosen for the survey covers 87·5 square miles. The total population in this area is 2,362, giving a mean population density of 0·04 per acre. 48 per cent. of the people live in three large villages, 21 per cent. in eleven smaller villages and hamlets, and the remaining 31 per cent. in scattered farms in the main dale and three branch dales.

The population of the Dale is slowly decreasing and there has been little new building. Nearly all the houses are built of local stone with stone floors. 63 per cent. are over 100 years old, 28 per cent. are between 10 and 100 years old, and only 9 per cent. are under 10 years old. 47·6 of the houses were classified as damp in a rural housing survey and in many this is only too obvious. The average number of persons per household is 3·04 and the average density per room is 0·61. A density of more than 2 per room was found in less than 4 per cent. of the houses (1951 Census report).

The age distribution of the population over the

age of 14 years is shown in Table I, where it is related to sex and place of birth. The small group born in neighbouring Dales came from an area within a radius of 7 miles from the head of the Dale, which is very similar to Wensleydale and with whose people there had always been a good deal of communication. This group is considered with the Dalespeople in later Tables. Among the men 77 per cent. belong to the Dales and 23 per cent. have come from other areas, and among the women 65 per cent. belong to the Dales and 35 per cent. come from other areas. Among the Dalespeople 46 per cent. of the men and 50 per cent. of the women are over the age of 44 years. Those coming from other parts of the country form an older population, 64 per cent. of men and 60 per cent. of women being over the age of 44 years. Among the Dalespeople, 65 per cent. of men and 79 per cent. of women had lived there all their lives. Those who had left the Dale for a time, had been away for a mean period of 8·7 years. Movement within the area was fairly common and many had lived in several farms or villages during their lives.

The majority of incomers had come as young adults, but 31 per cent. had been over the age of 40 years when they arrived. Among the men, 46 per cent., and among the women, 39 per cent., had lived in the Dale for less than 10 years, though 10 per cent. of men and 14 per cent. of women had lived there for more than 40 years.

Most of the people lead active lives. About 90 per cent. of the women are engaged solely in domestic work, and the remainder work in shops or hotels, or as clerks, teachers, or nurses. There is no difference between women born in the Dales and those from other areas in respect of occupation.

Among the men there is greater diversity of work. The majority of youths aged 15 to 19 years are engaged in farm service, and when this is finished a number of them are forced to leave the Dale to seek work elsewhere. Among those over the age of 19 years, 53 per cent. of Dalesmen and 27 per cent. of those from other areas are, or have been, farmers, farm-workers, or dairy-men. A similar proportion of Dalesmen (30 per cent.) and incomers (33 per cent.) are, or have been, employed in transport, road or railway maintenance, public services, building, or quarrying. Thus 83 per cent. of Dalesmen and 60 per cent. of incomers have led active outdoor lives, frequently exposed to wet. Trading occupies 14 per cent. of local men, and 12 per cent. of those from other areas, but only 3 per cent. of local men compared with 26 per cent. of those from other areas are, or have been, engaged in professional work.

At present, the economic state of the people is good, but many of the older ones can tell of long days worked for a very small wage on a diet consisting largely of bread and butter. Their diet still includes a great deal of bread and pastry, but is reasonably good, though lacking in fresh fruit and vegetables.

Method of Inquiry

The current Electoral Roll was used as a basis for defining the population, and was amended by personal inquiry during the course of the survey.

Before visiting in each of the three main villages and their surrounding districts, permission was sought to address the local Women's Organizations, to explain the purpose of the survey and to ask for

TABLE I

AGE DISTRIBUTION OF POPULATION OVER 14 YEARS RELATED TO SEX AND PLACE OF BIRTH

Age Group (yrs)	Place of Birth						Total	
	Wensleydale		Neighbouring Dales		Other Areas			
	Males	Females	Males	Females	Males	Females	Males	Females
15–24	126	96	5	16	17	34	148	146
25–34	92	74	14	22	15	37	121	133
35–44	101	79	20	23	37	61	158	163
45–54	105	73	23	21	46	57	174	151
55–64	67	77	12	14	25	54	104	145
65–74	60	59	3	14	32	59	95	132
75 +	24	31	9	6	22	32	55	69
No information	8	9	—	1	6	2	14	12
Total	583	498	86	117	200	336	870	951

co-operation. In addition, a letter was sent to all adults, shortly before they were visited, telling them of the proposed visit and again explaining the purpose of the survey.

At each house the number of occupants was recorded, and also certain particulars about the building. Information about age, sex, birthplace, length of residence in the Dale, past and present occupation, illnesses, and rheumatic complaints, was obtained about all over the age of 19 years. Inquiry was made concerning a family history of rheumatism, particularly among members of the household aged 15 to 19 years, and names and addresses of first-degree relatives living in the area were recorded.

During the first part of the survey, covering 66 per cent. of the population, 85 per cent. of the people over the age of 19 years were seen by the physician (J.M.B.). Those not seen were mostly young adults, about whom information was obtained from their relatives. During the remaining period, assistance was available from Miss Joan Hainsworth, Social Worker in the Empire Rheumatism Council Field Unit, and a number of people who gave no past or present history of rheumatism were not seen by the physician. During this period the ages of those between 15 and 19 years in each household were also recorded and later this information was obtained for the whole population.

All persons over the age of 14 years, with a history or complaint in any way suggestive of rheumatic disease, were seen by the physician, a more detailed history was taken, and a brief clinical examination of the joints was made. In all, information was obtained about 98·6 per cent. of the adult population.

This work was used in the selection of an area for a detailed survey, including radiological and serological investigation, by the Empire Rheumatism Council Field Unit. An area was chosen to give a representative sample of the population and to include half those considered to have inflammatory polyarthritis or generalized osteo-arthrosis. It was later enlarged to include two more areas of scattered farms, so that the Area Sample finally included nearly all the farms in the district, and consisted of 1,025 persons over the age of 14 years, of whom 891 (86·7 per cent.) were examined. The author took part in this work, and also re-examined 46 persons from the remaining districts who had definite or doubtful signs or a past history suggestive of inflammatory polyarthritis. These people were examined radiologically and gave blood for serological investigation.

At the clinical examination the joints were examined, the blood pressure was recorded, and a sample of blood was withdrawn.

X rays were taken, according to the following plan:

Age (yrs)	Site
15-34	Hands, feet, and cervical spine
35-54	As above, plus knees, and dorsal and lumbar spine
55 +	As above, plus pelvis

In a few cases the people were examined in their own homes with portable apparatus, and films of the dorsal and lumbar spine and the pelvis had to be omitted.

In the clinical and radiological examination five grades were recorded for each condition:

0 = None
1 = Doubtful
2 = Mild
3 = Moderate
4 = Severe

The sensitized sheep cell test (S.S.C.T.) was performed on sera from 858 persons (82·7 per cent.) in the Area Sample and from the 46 persons from the remaining districts described above, using the method of Ball (1950) in the laboratory of the Rheumatism Research Unit, University of Manchester.

In the present paper, the diagnoses are those made during the study of rheumatic complaints, confirmed or modified by radiological and serological evidence, in 91 per cent. of cases of inflammatory polyarthritis and in 61 per cent. of cases of other conditions. All films were read by one observer (J.M.B.). Radiological evidence of inflammatory polyarthritis does not include the changes in the cervical spine described by Sharp, Purser, and Lawrence (1958).

Results

Past Complaints

A number of people gave a history of some rheumatic complaint in the past.

Acute Disk Prolapse.—Among the Dalespeople, 5·5 per cent. of men and 1·7 per cent. of women and among those from other areas, 8·2 per cent. of men and 3·6 per cent. of women gave a history suggestive of an acute disk prolapse. In five women, this had occurred shortly after childbirth.

Past Polyarthritis.—Among the Dalespeople, four men (0·6 per cent.) and ten women (1·6 per cent.)

gave a history of joint pain and swelling lasting from a few weeks to a few months. In five women, the attack followed shortly after an infection. Two men and three women associated the illness with some physical or mental stress. In one woman it followed a miscarriage, and in another it occurred shortly after childbirth.

A similar history was given by two men (1 per cent.) and twelve women (3·5 per cent.) from other areas. Among these people, one man and six women had a history of preceding infection. The other man and three of the other women associated the episode with some stress.

In all cases the attack was mild and none had residual signs of arthritis. The mean age at the time of the attack was 35 years (range 10 to 77) and all had remained symptom-free for a mean period of 13·9 years (range 1 to 40). Radiological and serological investigation was carried out in seventeen cases (61 per cent.). None had evidence of erosive arthritis and none had a positive S.S.C.T.

Arthralgia associated with Erythema Nodosum.—Six Daleswomen gave a history of joint pains associated with an attack of erythema nodosum. In three cases, the joint symptoms lasted a few weeks only, in one case preceding the rash, but three had more persistent pains. One still had minimal symptoms, but no signs when she was seen, 7 years after her illness, but the others were symptom-free. Radiological examination in four cases showed no abnormalities in their joints, nor did they have a positive S.S.C.T. The mean age at the time of illness in this small group was 30·5 years (range 21 to 39) and the mean length of time since the attack was 7·9 years (range 1 to 15).

Present Complaints

Rheumatic Complaints.—The prevalence is shown in Table II, where it is related to age, sex, and place of birth. The diagnoses are not mutually exclusive. In some cases, one individual had evidence of more than one condition, the commonest association being between osteo-arthrosis and degenerative disk lesions. The complaints were mild in the majority of cases and only about 10 per cent. were seriously handicapped by their rheumatism.

Minor Complaints.—Minor aches and pains were mentioned by 12·9 per cent. of men and 11·7 per cent. of women born in the Dale, and by 11·2 per cent. of men and 9·6 per cent. of women from other areas. These pains were intermittent, but in some cases had recurred over a period of several years. People of all ages suffered from these pains, which fell into four well-defined groups:

(*i*) Pain in the shoulder. In some cases localizing signs could be found, but often they were absent.
(*ii*) Pains in the back or neck, usually in the upper dorsal region and associated with tenderness of the trapezius.
(*iii*) A variety of pains, in which no common factor could be found.

TABLE II

PREVALENCE OF RHEUMATIC COMPLAINTS

Age Group (yrs)	Place: In the Dales											
	No. in Group		Rheumatic Complaints									
			Inflammatory Polyarthritis		Osteo-Arthrosis				Disk Lesions		Other Conditions	
					Local		Generalized					
	M	F	M	F	M	F	M	F	M	F	M	F
15–34	237	208	3 (1·3)	1 (0·5)						1 (0·5)		2 (0·9)
35–54	249	196	6 (2·4)	15 (7·7)	25 (10)	10 (5·1)	4 (1·6)	9 (4·5)	20 (8)	13 (6·6)	4 (1·6)	3 (2)
55 +	175	201	6 (3·4)	27 (13·4)	24 (13·7)	25 (12·4)	20 (11·4)	65 (32)	22 (12·5)	22 (10·9)	4 (2·3)	3 (1·5)
No Information	8	10										
Total Seen	661	605	15 (2·3)	43 (7·1)	49 (7·2)	35 (5·8)	24 (3·7)	74 (12·3)	42 (6·4)	36 (5·9)	8 (1·4)	8 (1·8)

Numbers in brackets are percentages.

(*iv*) Recurrent mild joint pains. 22 men (3·4 per cent.) and 22 women (3·6 per cent.) born in the Dale, and three men (1·5 per cent.) and six women (1·8 per cent.) from other areas, complained of recurrent mild joint pains, with little swelling or stiffness, and no objective signs at the time of examination. In two men and nine women only the larger joints were affected, and these people were markedly weather sensitive. Among the others, the hands were frequently involved. Radiological examination in 52 cases showed no evidence of erosive arthritis, but thirteen had minimal signs of osteo-arthrosis. A positive S.S.C.T. was found in one Daleswoman and one incomer. The mean age at onset of symptoms was 35·6 years (range 10 to 81), and the mean duration was 4·7 years (range 1 to 18).

Though the prevalence of these complaints is higher among the Dalespeople, the differences between the groups are not significant ($p = >0·05$).

Other Conditions.—Included in this group are three men suffering from ankylosing spondylitis, and one case each of disseminated lupus erythematosus, gout, and psoriatic arthropathy.

There were two cases of juvenile rheumatoid arthritis, a man now aged 31 years, and a woman now aged 40 years. Both were Dalespeople, who had developed symptoms at the ages of 11 and 12 years respectively. Both had had considerable disability for 1 or 2 years, but had thereafter improved and now had minimal residual signs, though the woman continued to complain of joint pains. She had no abnormality of the joints *x*-rayed and her S.S.C.T. was negative. The man was not available for these tests.

In two cases, a Dalesman and an incoming woman, a diagnosis of psychogenic rheumatism was made. Both had been investigated in hospital where no objective evidence of disease had been found, and both admitted that their pains were worse when they were worried.

In two cases, no final diagnosis was made. One, a Dalesman aged 66 years, developed arthritis of the hips at the age of 27 years, and the other, an incoming woman aged 37 years, had developed a moderate arthritis of one knee at the age of 19 years. In both, radiological investigations showed only osteo-arthritic changes and the S.S.C.T. was negative.

Finally, a small group of twelve people (five men and seven women) complained of joint pains with little swelling or stiffness affecting the large joints, which had recurred ever since they had had an attack of rheumatic fever. None had objective signs of inflammatory polyarthritis, though four had signs of osteo-arthrosis. Radiological examination in eight cases showed no signs of erosive arthritis, though five had signs of osteo-arthrosis. None had a positive S.S.C.T. The mean age of these people at the time of their acute illness was 23 years (range 16 to 41) and the mean duration of

II

RELATED TO AGE, SEX, AND PLACE OF BIRTH

of Birth

				In Other Areas											
				Rheumatic Complaints											
Minor Complaints		No. in Group		Inflammatory Polyarthritis		Osteo-Arthrosis				Disk Lesions		Other Conditions		Minor Complaints	
						Local		Generalized							
M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
18 (8·9)	24 (11·5)	32	71	1 (3·3)	1 (1·4)						1 (1·4)	1 (3·3)	2 (2·8)	3 (9·9)	11 (15·4)
49 (19·6)	37 (18·8)	83	118	2 (2·4)	8 (6·9)	6 (7·2)	3 (2·5)	2 (2·4)	8 (6·7)	3 (3·6)	11 (9·3)	1 (1·2)	3 (2·5)	12 (14·4)	16 (13·4)
17 (9·6)	13 (6·5)	79	145	3 (3·8)	12 (8·3)	10 (12·6)	16 (11)	8 (10)	56 (38)	12 (12·6)	21 (14·5)	1 (1·3)		7 (8·8)	5 (3·4)
		6	2												
84 (12·9)	72 (11·7)	194	334	6 (3·1)	21 (6·3)	16 (8·2)	19 (5·7)	10 (5·1)	64 (19·1)	15 (7·7)	33 (9·9)	3 (2)	5 (1·5)	22 (11·2)	32 (9·6)

their joint symptoms was 28·6 years (range 15 to 33).

There is no significant difference between the Dalespeople and those from other areas in the distribution of these cases ($p = >0{\cdot}05$).

Osteo-Arthrosis and Degenerative Disk Lesions

Osteo-arthrosis giving rise to symptoms was found in 10·9 per cent. of men and 18·0 per cent. of women born in the Dale, and in 13·3 per cent. of men and 24·8 per cent. of women born in other areas. The prevalence of the localized form of the disease was higher among the younger Dalespeople, otherwise there was little difference between them and those coming into the Dale. The high overall prevalence of this condition may be related to the proportion of older people in this population, which is high, particularly among those coming into the Dale.

Symptoms due to degenerative disk lesions were found in 6·6 per cent. of men and 5·9 per cent. of women born in the Dale, and in 7·7 per cent. of men and 9·9 per cent. of women from other areas.

The true prevalence of these two conditions cannot be ascertained from symptomatic cases. It is to be reported and discussed more fully elsewhere (Lawrence and Bremner, in preparation).

Inflammatory Polyarthritis

Evidence of inflammatory polyarthritis was found in fifteen men (2·3 per cent.) and 43 women (7·1 per cent.) born in the Dales, and in six men (3·1 per cent.) and 21 women (6·3 per cent.) born in other areas. There is little difference between the sexes in the younger age groups, and the prevalence rises only slightly with age in both groups of men. There is a much greater rise with age among women, especially those born in the Dale. Of the incomers, eight (29 per cent.) had developed symptoms before they came to the district.

In Table III, these people are divided into different categories according to the evidence of disease which they show, and these are related to age, sex, and place of birth. Eight men (1·2 per cent.) and 23 women (3·8 per cent.) born in the Dale and two men (1 per cent.) and ten women (3·0 per cent.) from other areas, had evidence of inflammatory polyarthritis confirmed radiologically, with or without a positive S.S.C.T. One Daleswoman also had psoriasis. Among the Dalespeople seven men (1·1 per cent.) and seventeen women (2·8 per cent.), and among those from other areas three men (1·5 per cent.) and seven women (2·1 per cent.) had clinical signs of disease, without radiological signs or a positive S.S.C.T.

In addition, eight people who had clinical signs of the disease were not available for radiological or serological investigation. Of these, one Daleswoman had severe progressive disease, and another was moderately disabled. One woman from outside the area had mild but definite disease, and two others in this group, a man and a woman, had a history of considerable disability lasting 1 to 2 years, 16 and 8 years previously, with complete remission of symptoms but minimal residual signs. The remainder had very mild disease.

TABLE III

EVIDENCE OF INFLAMMATORY POLYARTHRITIS RELATED TO AGE, SEX, AND PLACE OF BIRTH

Age Group (yrs)	Place of Birth																					
	In the Dales												In Other Areas									
	No. in Group		Evidence of Disease										No. in Group		Evidence of Disease							
			Clinical and Radiological				Clinical		No Radiological or Serological Examination		Percentage of Age Group				Clinical and Radiological				Clinical		No Radiological or Serological Examination		Percentage of Age Group	
			Positive S.S.C.T.		Negative S.S.C.T.										Positive S.S.C.T.		Negative S.S.C.T.							
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
15–34	237	208			1		2	1			1·3	0·5	32	71					1	1			3·3	1·4
35–54	249	196		2	2	6	4	6		1	2·4	7·7	83	118	1			2	1	5		1	2·4	6·9
55 +	175	201		4	5	11	1	10		2	3·4	13·4	79	145		1	1	7	1	1	1	3	3·8	8·3
Total ..	661	605		6	8	17	7	17		3	2·3	7·1	194	334	1	1	1	9	3	7	1	4	3·1	6·3
Percentage ..				1	1·2	2·8	1·1	2·8		0·5					0·5	0·3	0·5	3	1·5	2·1	0·5	1·2		

There is no significant difference between the two groups in the prevalence of this disease, though it is higher in all categories among the older Dales-women.

In Table IV, certain features of inflammatory polyarthritis are shown in relation to the clinical, radiological, and serological evidence of disease.

In all categories the mean age at onset is similar, within a similar wide range. The mean duration also is similar, except among those showing only clinical signs of disease, a group which contains the largest number of early cases. Again, the range is wide, but similar for all categories. The proportion of cases with an acute onset is also similar in all except in those with only clinical signs, in which it is much lower.

In all, eight people (9·4 per cent.) had had their disease for too short a time for its course to be defined. Only six (8 per cent.) had rapidly progressive disease, and another small group of sixteen (19 per cent.) had had a series of exacerbations and remissions. The largest group, comprising 31 people (37·6 per cent), had mild disease which had deteriorated little over the years. Another fairly large group of 24 people (28 per cent.) had finally improved steadily after an initial illness lasting for varying periods. Among them, six men and five women form a well-defined group. All gave a history of severe disability lasting from 1 to 2 years, followed by gradual recovery to complete remission which had lasted for a mean time of 18·3 years (range 5 to 40). All had minimal residual signs when they were seen, and three had fairly severe clinical osteo-arthrosis. Radiological examination in nine cases showed signs of erosive arthritis in six and of osteo-arthrosis in seven. None had a positive S.S.C.T. at the time of examination. The mean age at onset in this group (46·4 years, range 23 to 64) was the same as that in the rest of the cases. Only four cases had had hospital treatment, and two others had been given gold. The rest had been treated at home. Seven were Dalespeople and four came from other areas.

At the time of examination, 62 people (74 per cent.) had mild disease, but a number had been much more severely ill in the past. Eighteen people (20 per cent.) had moderate disease, and only five people (6 per cent.) were severely affected. Their disease caused no disability in 49 people (57 per cent.) and a further 28 (33 per cent.) maintained their independence with varying degrees of difficulty. Seven people (8·2 per cent.) were to some extent dependent on others, but only one, a woman of 74 with a long history of rapidly progressive disease and a strongly positive S.S.C.T., was entirely incapacitated.

When these features are considered in relation to evidence of disease, those whose course tended to ultimate remission were present in similar proportions in all categories. In other respects, the small

TABLE IV

CLINICAL FEATURES OF INFLAMMATORY POLYARTHRITIS RELATED TO EVIDENCE OF DISEASE

Evidence of Inflammatory Polyarthritis	No. in Group	Mean Age at Onset (yrs) (Range)	Mean Duration (yrs) (Range)	Type of Onset		Type of Course					Severity of Disease			Grade of Functional Capacity			
				Sudden	Insidious	1	2	3	4	5	Mild	Moderate	Severe	1	2	3	4
Clinical Radiological Positive S.S.C.T.	8	49 (30–62)	11·8 (2–34)	3	5	2	1	2	3	0	1	4	3	0	5	2	1
Clinical Radiological	35	44·2 (17–79)	15·3 (1–51)	13	22	12	8	10	2	3	23	11	1	18	14	3	0
Clinical	34	42·2 (16–70)	8 (1–37)	6	28	7	7	16	0	4	32	2	0	27	7	0	0
No Radiological or Serological Examination	8	48·5 (37–68)	13·9 (1–30)	2	6	3	0	3	1	1	6	1	1	4	2	2	0
Total	85	44·5 (16–79)	11·9 (1–51)	24	61	24	16	31	6	8	62	18	5	49	28	7	1

KEY: *Types of Course*
1 = Steady improvement after initial attack
2 = Exacerbation and remission
3 = Slowly progressive
4 = Rapidly progressive without remission
5 = Undefined, as duration of symptoms too short.

Grades of Functional Capacity
1 = No disability
2 = Slight disability, but independent
3 = Moderate disability, with some dependence on others
4 = Marked disability, with complete dependence on others.

sero-positive group fared far worse than the others. They included half the cases with a rapidly progressive course, more than half those with severe disease, and nearly half those in the lower two grades of functional capacity.

In Table V the same features of inflammatory polyarthritis are shown in relation to sex. When the sexes were divided into those born in the Dale and those coming into the area, little difference was found except in the age at onset among males, which was much lower among the Dalesmen, twelve of whom (80 per cent.) had developed their disease before the age of 40 years. As they form the majority of the small group of men, the mean age at onset among males (39·8 years) is lower than that among females (46·7 years), though the range is the same in both sexes.

The proportion of those whose disease ran an ultimately more benign course is much higher among the men, of whom eleven (52 per cent.) had had a more or less complete remission of symptoms compared with thirteen women (23 per cent.). This difference between the sexes is significant ($p = <0·02$). None of the men had severe disease when they were seen, and none were dependent on others, though ten (48 per cent.) had been so at some time in the past. Among the women with little or no disability when they were seen, eight (12·5 per cent.) had been more seriously handicapped in the past.

In Table VI clinical and radiological signs of osteo-arthrosis are shown in relation to clinical, radiological, and serological evidence of inflammatory polyarthritis in those cases in which these investigations were performed. Clinical signs of osteo-arthrosis were found in 12·5 per cent. of the small sero-positive group, and in 14·3 and 14·7 per cent. of the two sero-negative groups. This is slightly lower than the prevalence in the general population (16 per cent.), but the numbers are small and the difference is not significant. Radiological evidence of osteo-arthrosis was mild in the majority of cases, and was found twice as frequently as clinical signs in all groups.

TABLE V

CLINICAL FEATURES OF INFLAMMATORY POLYARTHRITIS RELATED TO SEX

Sex	No. of Cases	Mean Age at Onset (yrs) (Range)	Mean Duration (yrs) (Range)	Type of Onset		Type of Course					Severity of Disease			Grade of Functional Capacity			
				Sudden	Insidious	1	2	3	4	5	Mild	Moderate	Severe	1	2	3	4
Male	21	39·8 (16–77)	12·4 (1–47)	7	14	11	5	4	0	1	16	5	0	16	5	0	0
Female	64	46·9 (17–79)	11·8 (1–51)	17	47	13	11	27	6	7	46	13	5	33	23	7	1
Total	85	44·5 (16–79)	11·9 (1–51)	24	61	24	16	31	6	8	62	18	5	49	28	7	1

KEY: *Types of Course*
1 = Steady improvement after initial attack
2 = Exacerbation and remission
3 = Slowly progressive
4 = Rapidly progressive without remission
5 = Undefined, as duration of symptoms too short.

Grades of Functional Capacity
1 = No disability
2 = Slight disability, but independent
3 = Moderate disability, with some dependence on others
4 = Marked disability, with complete dependence on others.

TABLE VI

CLINICAL AND RADIOLOGICAL SIGNS OF OSTEO-ARTHROSIS ASSOCIATED WITH INFLAMMATORY POLYARTHRITIS

Evidence of Inflammatory Polyarthritis	No. in Group	Radiological Signs				Clinical Osteo-Arthrosis	
		None	Erosive Arthritis	Erosive Arthritis + Osteo-Arthrosis	Osteo-Arthrosis	No.	Per cent.
Clinical Radiological Positive S.S.C.T.	8		6	2		1	12·5
Clinical Radiological	35		25	10		5	14·3
Clinical	34	26			8	5	14·7
Total	77	26	31	12	8	11	14·2

The Sensitized Sheep Cell Test

This test was performed on sera from 392 males and 466 females in the Area Sample and from the 46 persons in the remaining districts described previously. The test was positive in two of the latter, both of whom had definite inflammatory polyarthritis.

The distribution of positive tests among persons in the Area Sample is shown in Table VII, where it is related to age, sex, and place of birth. The test was positive in sera from five men (1·3 per cent.) and fifteen women (3·2 per cent.). Four of the five men were Dalesmen; none had evidence of inflammatory polyarthritis, but two of the four were relatives of people with definite or doubtful signs of the disease. The remaining man was a Belgian, who had lived for many years in the Dale and who had longstanding inflammatory polyarthritis. Among the women, eight (2·8 per cent.) had been born in the Dale. Of these, five had definite inflammatory polyarthritis and one had had several episodes of arthralgia. The remaining two women had no clinical or radiological signs of the disease, but one was the daughter of a woman with severe sero-positive arthritis. Among the seven women (3·8 per cent.) who came from other areas, one had doubtful clinical signs of inflammatory polyarthritis and two had doubtful radiological signs of the disease. The remainder had no evidence of the disease.

The prevalence of a positive S.S.C.T. is thus lower among males than among females, and does not rise with age among them as it does among the women. Among the Daleswomen, the prevalence is equal (5 per cent.) in all age groups over the age of 45 years. Among women coming from other areas, the total prevalence is slightly higher, and rises more sharply to 9 per cent. in the oldest age group.

The numbers are too small for the differences to be significant.

Occupation and Rheumatic Complaints

In this population, there were no occupational differences among the women. Among the men, the different occupational groups are represented among those with inflammatory polyarthritis in the same proportions as among the general population. Osteo-arthrosis occurred in a higher proportion of farmers, and disk lesions somewhat more frequently among road-workers, railway gangers, and quarrymen, than in the rest of the population. The differences are not large enough to be significant.

Discussion

The two groups within this population differ in several respects. The Dalespeople have lived in the same environment for the greater part of their lives, and many share a common heredity. Those who have come to the Dale have come from all parts of the country. Nearly half have lived there for a relatively short time and nearly one-third were over the age of 40 years when they arrived. It may be supposed, therefore, that, for the majority, their principal environment would be different from

TABLE VII

DISTRIBUTION OF A POSITIVE S.S.C.T. IN THE AREA SAMPLE IN RELATION TO AGE, SEX, AND PLACE OF BIRTH

Age Group (yrs)		Place of Birth							
		In the Dales				In Other Areas			
		Males		Females		Males		Females	
		No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive	No. Tested	No. Positive
−24		50	2	48	—	17	—	21	—
−34		48	—	42	1	9	—	23	1
−44		57	2	50	—	17	—	39	1
−54		55	—	40	2	25	1	34	—
−64		35	—	37	2	14	—	24	1
65+		42	—	64	3	23	—	44	4
Total	No. ..	287	4	281	8	105	1	185	7
	Per cent. ..		1·4		2·8		0·9		3·8

their present surroundings and it is certain that few share any hereditary factors.

There is less difference between the groups in respect of occupation. Men coming to the Dale form the majority of the small group of professional workers in the district, and few are engaged in farming, but in other respects there is little difference between the groups.

Only minor differences were found in the prevalence of rheumatic complaints in these two groups. In both, the prevalence of inflammatory polyarthritis and disk lesions among males, and of minor complaints in both sexes, shows no significant difference from that found by Kellgren, Lawrence, and Aitken-Swan (1953) in Leigh. The prevalence of inflammatory polyarthritis among both groups of women is higher than in Leigh, significantly so in the case of the Daleswomen. This may be partly due to the fact that the women in the Dale are an older population than that particular sample of the population of Leigh. This may also be a factor in the higher prevalence of osteo-arthrosis and disk lesions among them. That this may be so is suggested by the closer agreement shown between the figures for inflammatory polyarthritis and generalized osteo-arthrosis in the oldest age group in the present study and those in Table II in the report by Kellgren and Lawrence (1956) of a study of the 55 to 64 age groups in Leigh. The figures for "confirmed" inflammatory polyarthritis among males are similar to those found by Miall, Ball, and Kellgren (1958) among men in South Wales. Higher figures were found among both groups of women in the Dale than were found in South Wales, the difference being significant in the case of women in the Rhondda. These observations in four very different districts suggest that there is little variation in the prevalence of inflammatory polyarthritis among males, but that more marked differences occur among women. However, the fact that there is no significant difference between the Daleswomen and a group of women from many parts of the country suggests that these variations, at least in Great Britain, are nowhere very large.

The fact that comparison between a population in which many people are related, and one in which there can be no common hereditary factors, has shown no significant difference in the prevalence of inflammatory polyarthritis suggests that genetic influences do not play a large part in determining its prevalence. This is of interest in view of the familial aggregation in this condition shown by several workers (Barter, 1952; Stecher, Hersh, Solomon, and Wolpaw, 1953; Miall, 1955; Lawrence and Ball, 1958).

The small group with joint symptoms associated with erythema nodosum illustrates several of the points made by Truelove (1960), though his finding of a high prevalence of low-titre agglutination in the S S.C.T. was not confirmed in those in whom the test was done. The people who complained of persistent joint pains after rheumatic fever form a well-defined group. They show some of the clinical features of "chronic rheumatic fever" described by Thomas (1955), but not the radiological changes in the spine. Those persons who gave a history of a brief episode of joint pains are a more homogeneous group than that described by Lawrence and Bennett (1960) as suffering from "benign polyarthritis", but their long period of freedom from symptoms would entitle them to that designation.

The clinical picture of inflammatory polyarthritis found in this population differs from that seen in hospital practice. The low prevalence of arthritis associated with a positive S.S.C.T. (19 per cent. in those with radiological signs) contrasts with 60 to 80 per cent. found in most hospital series. However, the more serious prognosis associated with a positive S.S.C.T. found by Duthie, Brown, Knox, and Thompson (1957) is strikingly confirmed. The better prognosis among men found by these workers and by Short, Bauer, and Reynolds (1957) is also confirmed. It is possible that the low prevalence of a positive S.S.C.T. among men in this population is associated with their more benign disease. A group of particular interest is that with an acute onset of severe disease with ultimate complete remission. One may note the similarity of their history to that of the group of cases admitted within one year of onset, described by Duthie and others (1957), in whom a similar benign outcome was found. Lewis-Faning (1945), Lewis-Faning and Fletcher (1945), and Short, Bauer, and Reynolds (1957) also reported a better prognosis in cases admitted to hospital within one year of onset. The latter workers comment that there is insufficient evidence to conclude that this is the result of treatment, rather than the natural course of that particular form of the disease. The fact that only two of the eleven people in this group had in-patient treatment, yet all did well, supports this opinion.

The distribution of a positive S.S.C.T. in that part of the population included in the Area Sample, does not conform closely to the pattern described by Kellgren and Lawrence (1956), and Lawrence and Ball (1958), who found an equal prevalence in both sexes, and an overall prevalence of 5 per cent. in all over the age of 14 years, rising to 13 per cent. in those aged 65 years and over, in samples of the population of Leigh. The total prevalence is lower,

particularly among the Dalespeople, and among both groups of men, among whom the rise with age is not seen. The closest resemblance is found among women coming into the Dale. The numbers are small, but the fact that considerable differences were found in the prevalence of a positive S.S.C.T. in two recent studies of relatives of persons suffering from inflammatory polyarthritis (Lawrence and Ball, 1958; Bremner, Alexander, and Duthie, 1959) suggests that such variations are not rare.

This account of rheumatic complaints in a rural community shows how common they are and how mild in the majority of cases. Among the Dalespeople, the outstanding features are the early onset and benign course of inflammatory polyarthritis among males and the close association of a personal or family history of clinical inflammatory polyarthritis among those with a positive S.S.C.T., of whom 50 per cent. had definite or doubtful clinical disease, and a further 25 per cent. had relatives suffering from it. This observation contrasts with those in some other populations, in one of which only 17 per cent. of those with a positive S.S.C.T. had clinical disease (Lawrence, 1960). Miall, Ball, and Kellgren (1958) comment on the milder character of the cases of inflammatory polyarthritis which they saw in the Vale of Glamorgan, another rural area, when compared with those in the Rhondda. It is possible that study of such variations in clinical course in different areas, may help to throw light on the nature of this disease.

Summary

(1) A survey of rheumatic complaints was carried out in a rural area of Yorkshire with a population of 1,821 people over the age of 14 years. The results were used in the selection of an Area Sample, which was investigated radiologically, serologically, and clinically by the Empire Rheumatism Council Field Unit. This sample consisted of 1,025 persons over the age of 14 years of whom 891 were examined.

(2) The people were divided into two groups, those born in the Dale and those coming into the district. No significant difference was found in the prevalence of rheumatic complaints in these two groups, nor between them and other reported population studies.

(3) Some features of inflammatory polyarthritis were considered in relation to sex and to evidence of disease. An earlier onset and a better prognosis was found among men. The small group with arthritis associated with a positive S.S.C.T. fared worse than all other groups.

(4) The results are discussed in relation to other population studies and studies of the course of inflammatory polyarthritis.

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Manifestations rhumatismales dans une population rurale

RÉSUMÉ

(1) On a procédé à une enquête sur les manifestations rhumatismales dans une zone rurale de Yorkshire, ayant une population de 1.821 personnes âgées de plus de 14 ans. On s'est servi de résultats obtenus pour déterminer l'Echantillon de la Zone, qui a été étudié du point de vue clinique, sérologique et radiologique par un organe (*Field Unit*) de l'*Empire Rheumatism Council*.

Cet échantillon consistait de 1.025 personnes âgées de plus de 14 ans; 891 d'entre elles ont été examinées.

(2) La population a été divisée en deux groupes, ceux nés dans la vallée et ceux venus d'ailleurs. On n'a pas noté de différence appréciable en ce qui concerne la fréquence des manifestations rhumatismales entre les deux groupes, ni entre ces groupes et d'autres relevés dans les rapports sur des enquêtes similaires.

(3) On considère certains traits de la polyarthrite inflammatoire par rapport au sexe et à la symptomatologie. Un début à un âge plus jeune et un pronostic meilleur a été observé chez les hommes. Le petit groupe avec l'arthrite et une réaction positive d'agglutination des érythrocytes sensibilisés de mouton allait pire que les autres groupes.

(4) On discute les résultats par rapport aux autres enquêtes sur la fréquence morbide et aux études de l'évolution de la polyarthrite inflammatoire.

Manifestaciones reumáticas entre una población rural

SUMARIO

(1) Una investigación de las manifestaciones reumáticas fué llevada a cabo en un area rural de Yorkshire con una población de 1.821 individuos de edad superior a 14 años. Los resultados se utilizaron para la selección de una Muestra de Zona, que fué investigada clínica, serológica y radiológicamente por un grupo (*Field Unit*) del *Empire Rheumatism Council*. Dicha muestra consistió de 1.025 personas de edad superior a 14 años de las cuales 891 fueron examinadas.

(2) La población se dividió en dos grupos, los nacidos en Dale y los demás. No se apreció diferencia significativa en cuanto a la frecuencia de manifestaciones reumáticas entre dichos grupos, ni entre ellos y los encontrados en otros estudios de poblaciones.

(3) Algunos rasgos de la poliartritis inflamatoria se consideran en relación con el sexo y la evidencia de enfermedad. Un comienzo más temprano y un mejor pronóstico fué encontrado en varones. El pequeño grupo con artritis y una reacción de aglutinación de eritrocitos sensibilizados de carnero positiva presentó un peor pronóstico que los demás grupos.

(4) Se discuten los resultados en relación con otros estudios de la incidencia de enfermedad entre poblaciones y con estudios de la evolución de la poliartritis inflamatoria.

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A CONTROLLED TRIAL OF PHENYLBUTAZONE, OXYPHENBUTAZONE, AND A PLACEBO IN THE TREATMENT OF RHEUMATOID ARTHRITIS

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In the past 10 years phenylbutazone (Butazolidin) has been recognized to be of value in the treatment of many painful musculo-skeletal disorders. Currie (1951, 1952) reported favourably, but after initial enthusiasm, it became evident that many side-effects could result. It is now generally accepted that its pain-relieving properties make it particularly useful in chronic disorders of bones and joints. The fact that up to 25 per cent. of patients given phenylbutazone react adversely to it, led to much research to find a similar substance which would be less toxic.

Several derivatives of phenylbutazone were detected in the urine of patients receiving the drug (Burns, Gutman, Yu, Paton, Perel, Steele, and Brodie, 1955a; Burns, Rose, Goodwin, Reichenthal, Horning, and Brodie, 1955b), and two of these have been synthesized. One of these, sulphinpyrazone (Anturan), a potent uricosuric agent, now has a definite place in the treatment of gout, and another, oxyphenbutazone (Tanderil),* which is also a naturally occurring metabolite of phenylbutazone, was the subject of this trial. Hart and Burley (1959), comparing oxyphenbutazone with phenylbutazone, found that the new substance was less liable to produce gastro-intestinal disturbance, but was somewhat less potent therapeutically. Other investigations, notably those of Mason and Cramer (1959), Cardoe (1959), and Graham (1960), reported substantially similar findings. Vaughn, Howell, and Kiem (1959) reported rather superior analgesic effects with oxyphenbutazone and noted only one important side-effect: initial salt and water retention.

* Chemical name: hydroxyphenylbutazone.
Official name (Pharmacopoeal Commission): oxyphenbutazone.
Trade name: Tanderil, sometimes known as G.27202.

The majority of side-effects of phenylbutazone occur in the first month and, not infrequently, in the first week. Sperling (1959) remarked that the incidence of side-effects was higher in rheumatoid arthritis than in other disorders. It was, therefore, decided that it would be useful to investigate oxyphenbutazone in rheumatoid arthritis over a short period. Previous experience of a double-blind trial (Ansell, Fearnley, Bywaters, and Meanock, 1953) suggested that this method of a short-term trial would be a satisfactory approach in a disorder where over longer periods the natural history is punctuated by fluctuations in severity.

General Design of the Trial

The trial was designed to compare the response of patients with rheumatoid arthritis to three substances—phenylbutazone, oxyphenbutazone, and a placebo—not by administering each of the substances to a different group of patients, but by giving to sixty patients all three substances successively. Each patient served as his own control, so that for each the trial lasted 9 weeks, made up of three 3-week periods, during each of which one of the three substances was given.

During the year July, 1959, to June, 1960, patients were selected from those attending the out-patient department of the Rheumatology Unit of the Royal Berkshire Hospital, Reading, the criteria for inclusion being that they had had bilateral involvement of the wrists and hands for at least one year, were not over 75 years of age, and had a positive sheep-cell agglutination test and a raised erythrocyte sedimentation rate. In the two weeks before the trial, no treatment was given except that the patients

were allowed to take aspirin as required. At the beginning and end of this fortnight, assessments were made to ensure that no major fluctuations were occurring.

Corresponding to the six possible orders of administration (BPT, BTP, PBT, PTB, TBP, TPB) there were six groups, each planned to comprise ten patients (total entrants to the trial = 60). Here and elsewhere, B = phenylbutazone; T = oxyphenbutazone; P = placebo.

Sixty bottles of each substance (each containing 168 tablets, sufficient for 3 weeks' treatment) were supplied to the chief pharmacist before the start of the trial. Although the three types of tablet were not identical, they were all coloured white and the bottles were labelled merely:

A TABLETS (*or* B tablets *or* C tablets)
Two tablets to be taken four times per day

The phenylbutazone and oxyphenbutazone tablets each contained 100 mg. active ingredient. The total daily dose of each of these substances was thus 800 mg.

A blank register of sixty treatment sequences (BPT, BTP, etc.) numbered 1 to 60, but randomized for sequence, was lodged with the pharmacist. Each of the six orders or sequences appeared ten times.

As each patient entered the trial he was given a number (serially) by the clinician and sent to the pharmacist, who entered the patient's name in the register opposite the appropriate numbered sequence. This automatically determined the sequence in which the substances were to be given and each substance was ticked off on the list as issued to the patient (one 3-week period at a time). Thus the register held by the pharmacist (and which had been independently prepared by the statistician) was the only key to the order of treatments. At no time during the trial did the clinician or the patient know which treatment was being, or had already been, received.

Assessments

Assessments were recorded for each patient on a standard form. They were made at the beginning of the trial and at the end of each 3-week period when the patient attended for a further supply of tablets.

Four indices were used to judge progress. Only one was objective and quantitative, namely, strength of grip. The others were the patients' own assessments of degree of pain and of freedom of movement, and the physician's estimate of functional capacity in five grades. In addition to these assessments of progress, toxic and other side-effects were inquired for and recorded, together with reasons for ceasing to take the tablets where this occurred, and at the end of the trial, patients stated their order of preference for the three types of tablet.

Further details of these indices are given in the sections allotted to each.

Characteristics of the Entrants

In therapeutic trials, where one group of patients receives Drug A, another group Drug B, and so on, it is imperative to ensure that the groups are at the outset similar as regards relevant characteristics (age, sex, severity of disease, etc.). This is avoided in trials, as this one, where the patients serve as their own controls, but it is necessary nevertheless to describe the principal characteristics of the patients who took part.

Of the sixty entrants admitted to the trial (eleven males and 49 females), the ages ranged from 22 to 75 years (average 52·8; standard deviation 11·7). The duration of disease ranged from 1 to 17 years (average $5 \cdot 31 \pm 0 \cdot 54$). Judged by functional status (physician's estimate) the disease was of Grade 2* severity in 37, Grade 3 in 21, and Grade 4 in two. The mean Westergren erythrocyte sedimentation rate was 42·8 mm./hr, and the mean haemoglobin level 11·7 g. per cent. (see last column of Table I).

Similarity of Six "Order of Treatment" Groups

It was impracticable to secure at the outset that the six "order of treatment" groups would be similar in regard to these characteristics. In the event, however, the only significant difference found was in relation to the erythrocyte sedimentation rate. Here the ten patients who started on the placebo and finished on phenylbutazone had the lowest mean E.S.R. (32·7 mm./hr), whilst the group who started on phenylbutazone and finished on oxyphenbutazone had the highest (50·8 mm./hr). Between these two extremes appeared the only significant difference at the 0·05 level. In regard to all the other characteristics listed in Table I (opposite), the "order of treatment" groups were similar.

Numbers at Risk for Assessment of Side-Effects

For three patients, the only assessment was that made on completion of the first 3-week period. Two of these failed to attend subsequently (one because of pregnancy) so that in both patients side-effects

* For definitions of grades, see section on functional status.

TABLE I

SIMILARITY OF THE SIX "ORDER OF TREATMENT" GROUPS

Order of Treatment	TBP(*)	TPB	BTP	BPT	PTB	PBT	All Groups Combined
Total Entrants	10	10	10	10	10	10	60
Males	2	3	1	2	1	2	11
Mean Age (yrs)	51·8	51·8	53·9	48·7	52·8	57·9	52·8
Mean Duration of Disease (yrs)	5·1	4·4	5·0	4·3	7·4	5·6	5·3
Mean Strength of Grip: Right	126·0	140·5	141·5	118·5	124·5	149·5	133·4
Left	156·0	150·5	117·5	107·5	141·5	142·0	135·8
Mean Haemoglobin Concentration (g. per cent.)	11·4	11·8	11·7	11·5	12·1	11·5	11·7
Mean(†) E.S.R. (mm./hr Westergren)	46·1	39·1	48·4	50·8	32·7	39·4	42·8
Mean(‡) Functional Capacity (Physician's Assessment)	2·5	2·3	2·3	2·2	2·8	2·4	2·4

(*) B = phenylbutazone (Butazolidin); T = oxyphenbutazone (Tanderil); P = calcium phosphate, maize starch, etc. (placebo).
(†) Excludes one patient in group PBT (E.S.R. not stated).
(‡) Use of the term "Mean" here is unjustifiable statistically, but convenient as an index to summarize the distribution.

were not recorded on phenylbutazone or the placebo. The third was admitted to hospital after the first assessment (on placebo) for operation on an ankle joint and neither phenylbutazone nor oxyphenbutazone was given (see Table II).

Five patients were withdrawn because of toxic effects. In consequence, four were not assessed for side-effects on phenylbutazone, one was not assessed on oxyphenbutazone, and three were not assessed on placebo.

This left 53 at risk to side-effects on phenylbutazone, 58 on oxyphenbutazone, and 55 on placebo (Table II).

TABLE II

NUMBERS AT RISK FOR ASSESSMENT OF SIDE-EFFECTS

Drug		*B*	*T*	*P*
Total Entrants		60	60	60
Side-effects NOT recorded because of:	(1) Failure to attend for assessment	2	—	2
	(2) Admission for operation on ankle	1	1	—
	(3) Withdrawal on earlier treatments	4	1	3
Number at Risk for Side-effects		53	58	55

Results

TOXICITY

The incidence of side-effects can be measured in one of two ways:

(*i*) as the number of persons who experienced at least one side-effect—expressed as a percentage of the number at risk,

or

(*ii*) as the number of side-effects recorded per patient at risk on each drug.

(i) Persons experiencing at least One Side-Effect

Side-effects were reported by 28 per cent. of the patients on phenylbutazone (15 out of 53 at risk), by 31 per cent. on oxyphenbutazone (18 out of 58 at risk), and by 31 per cent. on placebo (17 out of 55 at risk).

These side-effects fall into three severity grades according as they necessitated (*a*) cessation of tablets (and in some instances no subsequent medicaments were taken); (*b*) reduction in dosage; (*c*) no action (Table III).

TABLE III

PATIENTS WITH SIDE-EFFECTS, BY GRADE OF SEVERITY

Drug		*B*	*T*	*P*
Side-effects involving:	(*a*) Cessation of tablets	3	4	4
	(*b*) Reduction of dosage	2	3	1
	(*c*) Neither (*a*) nor (*b*)	10	11	12
Patients with at least One Side-effect	No.	15	18	17
	Per cent.	(28)	(31)	(31)
No. of Patients without Side-effects		38(*)	40	38(†)
Total at Risk for Side-effects		53	58	55

(*) Includes one patient who became so much worse on phenylbutazone that he "gave up and went back to codeine".
(†) Includes one patient who found the placebo tablets (first period) useless and took solprin instead.

(*a*) *Cessation of Tablets* (*11 patients*)

PHENYLBUTAZONE (3 patients)

(1) Severe dermatitis after 12 days' treatment in the first 3-week period. Neither oxyphenbutazone nor the placebo was given subsequently.
(2) Nausea and abdominal pain after 10 days in the middle 3-week period.
(3) Experienced nausea and indigestion on placebo (first period), developed sore throat and ulcer of tongue on oxyphenbutazone (second period),

had recurrence of sore throat on phenylbutazone (third period). The side-effects in the first two periods are included under (*c*) in Table III.

OXYPHENBUTAZONE (4 patients)

(1) Patient paid a special visit after 10 days on the drug in the second period because of severe vomiting and diarrhoea, and the trial was stopped. Phenylbutazone was not given subsequently.
(2) Severe reaction reported at the end of the first period (oedema of face, generalized urticarial skin reaction). Neither phenylbutazone nor placebo was given. The rash was still present one month later.
(3) Severe mouth ulcers developed in the first period and the tablets were stopped. Although the patient went on to take placebo tablets in the second period, the ulcers recurred with cervical glandular enlargement. The patient was withdrawn from the rest of the trial and the side-effects were assumed to arise from the oxyphenbutazone.
(4) This patient had to stop after 10 days in the final period because of indigestion. However, in the first period on phenylbutazone she had experienced flatulence and dyspnoea, and had had to reduce the dosage.

PLACEBO (4 patients)

(1) Had developed mild indigestion after meals—lasting 2 to 3 hours, on oxyphenbutazone in the first period. In the second period on placebo the trial was stopped after 10 days. The general practitioner reported "fever, sore throat, oedema of legs, white blood count 8,400 per c.mm.".
(2) Tablets stopped after 2 weeks in the first period because of severe indigestion.
(3) Headache and severe nausea in the second period.
(4) Tablets stopped after 2 weeks in the second period because of headache and blurred vision.

(*b*) *Reduction of Dose* (*6 patients*)

PHENYLBUTAZONE (2 patients)

(1) First period—flatulence and dyspnoea—tablets reduced to four a day (see also Section (*a*)—Oxyphenbutazone (No. 4)).
(2) First period—diarrhoea—tablets reduced to six a day.

OXYPHENBUTAZONE (3 patients)

(1) Third period—headaches persisted until tablets reduced to six a day.
(2) Second period—nausea, vomiting—reduced to six for last week.
(3) First period—nausea, vomiting, diarrhoea—4 tablets a day after 4 days.

PLACEBO (1 patient)

First period—indigestion, dyspnoea, palpitation on effort—reduced dose.

(ii) Mean Number of Side-Effects per Patient

Some patients experienced more than one side-effect whilst on a specified treatment. The fifteen patients with side-effects whilst on phenylbutazone reported altogether eighteen such effects (three recorded two). The eighteen who had side-effects whilst on oxyphenbutazone recorded 22 such effects (two listed two, and one listed three). The seventeen who had side-effects whilst on the placebo tablets recorded 24 such effects (five listed two and one listed three).

Relating these to the total patients at risk on each drug (see foot of Table IV) the mean number of side-effects was 0·34 per person for phenylbutazone, 0·38 for oxyphenbutazone, and 0·44 for the placebo (no significant difference at the 0·05 level).

These side-effects are classified under general headings in Table IV (opposite). The numbers are too small for firm conclusions, but it appears that approximately one-third of the side-effects occurring on phenylbutazone and the placebo, and half of those occurring on oxyphenbutazone affected the gastro-intestinal system. Only one instance of buccal ulcers or sore throat was recorded on phenylbutazone, four on oxyphenbutazone, and two on the placebo. Oedema of the ankles was recorded more frequently on the placebo (five instances) than on phenylbutazone (four) or oxyphenbutazone (two).

Side-Effects while on Placebo.—Twenty patients received the placebo in the first 3-week period, and nine side-effects were reported by six of them.

Eighteen received the placebo in the second period, and twelve side-effects were reported by eight of them.

Seventeen received the placebo in the third period, but only three side-effects were recorded by three patients.

Thus, side-effects on the placebo were recorded by 30 per cent. of the patients who received it as the first, by 50 per cent. of those who received it as the second, and by only 18 per cent. of those who received it as the third drug. Also, of all the 24 side-effects observed whilst the patients were having placebo tablets, 37 per cent. occurred when it was the first drug given, 50 per cent. when it was the second, and 13 per cent. when it was the third.

If the placebo complications were residual effects from earlier treatments in the trial, one would expect them to be non-existent when the placebo was issued first. Yet 30 per cent. of the patients

TABLE IV

CLASSIFICATION OF SIDE-EFFECTS RECORDED BY PATIENTS ON THE THREE TREATMENT SCHEDULES

Side-Effects Recorded			Treatment B	Treatment T	Treatment P
Gastro-intestinal Reactions	Loss of appetite		—	—	1
	Nausea		1	2	2
	Epigastric distress		3	5	4
	Vomiting		—	3	—
	Diarrhoea		2	2	—
Skin Reactions	Mild dermatitis		1	—	1
	Severe dermatitis		1	1	1
Oedema	Ankles		4	2	5
	Swelling of eyelids		1	—	—
Ocular Reactions	Blurred vision		1	—	1
	Glaucoma		—	1	—
Miscellaneous Reactions	Objective	Buccal ulcers	—	3	—
		Sore throat	1	1	2
	Subjective	Headache	—	2	2
		Giddiness	2	—	3
		Dyspnoea	1	—	—
		Fever	—	—	1
		Palpitation	—	—	1
Total Side-effects			18	22	24
No. of Patients recording these Side-effects (see Table III)			15	18	17
No. of Patients at Risk			53	58	55
Side-effects per Patient at Risk			0·34	0·38	0·44

who had it in the first period experienced 37 per cent. of all the "placebo side-effects". Add to this the fact that, in the final period when residual effect, if any, might be expected to be most pronounced, 18 per cent. of patients accounted for only 13 per cent. of placebo side-effects (the lowest incidence for the three periods). There seems to be little evidence that the side-effects on the placebo tablets were residual manifestations of reactions which started during phenylbutazone or oxyphenbutazone treatment.

It is certainly curious that five instances of oedema should have occurred whilst the patient was having placebo tablets. Two of these occurred in the initial period, the previous treatment having been chloroquine and aspirin for one, and aspirin only for the other. The remaining three occurred in the middle period. In two of these, the placebo followed phenylbutazone, which had been taken without side-effects; unfortunately no record was made of how long after the end of the first period the onset of oedema occurred. In the third patient, it is known that the onset of oedema occurred within 10 days of the end of the first period on oxyphenbutazone. But, except for this last instance, and certainly not as regards the two instances in the initial period, oedema of the ankles cannot be ascribed to any drug. In most drug trials, oedema has been regarded as a side-effect of the drug. Present findings remind us that it is often a feature of the disease.

Gastro-intestinal Reactions.—Mason and Cramer (1959) found that, of thirteen patients unable to tolerate phenylbutazone because of gastro-intestinal reactions (dyspepsia, nausea, and diarrhoea), nine were able to tolerate oxyphenbutazone. The data were in agreement with this finding. In the present survey, we were able to confirm this finding. 29 patients received phenylbutazone before oxyphenbutazone (orders BPT, BTP, and PBT); six recorded gastro-intestinal side-effects on phenylbutazone, and only one of the six was unable to tolerate oxyphenbutazone for the same reason.

On the other hand, 23 patients received oxyphenbutazone before phenylbutazone (orders PTB, TBP, and TPB); only two recorded gastro-intestinal effects on the former, and both of them subsequently tolerated phenylbutazone.

STRENGTH OF GRIP

One important aspect to be considered in trials in which different treatments are given in succession to the same patients is the hangover or residual effect of the previous treatments. The only objective and quantitative index lending itself to numerical manipulation was strength of grip and the assessment of residual effects was mainly derived from analysis of these data.

The strength of grip of each hand was measured (in mm. Hg) at each assessment on a sphygmomanometer, with an initial bag pressure of 30 mm. Hg maintained for 3 seconds, the hand being held away

from the body. The grip at the end of each 3-week period, expressed as a percentage of the initial (pre-trial) value, gave an index of improvement (or deterioration) in grip in each treatment as compared with the pre-trial level.

Since estimation of the residual effects of previous treatments on these results involved the use of somewhat sophisticated statistical procedures, only the results are reported here, details and discussion of the method being relegated to the Appendix.

From this detailed statistical analysis of variance the following conclusions were relevant:

(*i*) There was great variation between patients in the amount of improvement on each drug. Such individual variation was, of course, to be expected.

(*ii*) The order in which the three treatments were given did not affect the results, *e.g.* the mean improvement on phenylbutazone did not vary significantly whether it was the first, second, or third treatment.

(*iii*) There was no evidence of any secular trend in the results. Irrespective of type of treatment, the average improvement in the right grip was 17·6 per cent. for the first period, 15·8 per cent. for the second, and 21·1 per cent. for the third. Comparable figures for the left grip were 15·8 per cent., 13·9 per cent., and 21·5 per cent.

(*iv*) It could be definitely stated that the residual effects of previous treatments (within the trial) were negligible. The amount of variation due to residual effects was not greater than would be expected merely from chance, and this was true of both left and right grip. In consequence, the adjustments required to allow for residual effects when comparing the *direct* results of the three treatments were also negligible, as is shown in Table V.

TABLE V

MEAN IMPROVEMENT IN GRIP STRENGTH (per cent.)

Treatment	Right		Left	
	Unadjusted Means	Adjusted for Residual Effects	Unadjusted Means	Adjusted for Residual Effects
Phenylbutazone ..	27·9	28·0	22·4	22·1
Oxyphenbutazone ..	23·4	24·4	20·3	20·8
Placebo	8·4	7·4	7·9	7·8
Standard Error of Differences (see Appendix) ..	4·53	5·06	5·49	6·13

The right grip improved to a greater extent than the left on both drugs, but not on the placebo. Possibly this is related to the greater use of the right hand generally, and suggests that activity plus drug treatment gives better results than drug treatment alone.

The mean differences between the three treatments as regards improvement in grip are shown in Table VI.

TABLE VI

MEAN DIFFERENCES BETWEEN THE TREATMENTS AS REGARDS PERCENTAGE IMPROVEMENT IN GRIP STRENGTH

Treatment	Right	Left
Phenylbutazone and Oxyphenbutazone (B-T)	3·6	1·3
Phenylbutazone and Placebo (B-P)	20·6s	14·3s
Oxyphenbutazone and Placebo (T-P) ..	17·0s	13·0s

s = Significant difference.

The right grip improved 21 per cent. more on phenylbutazone and 17 per cent. more on oxyphenbutazone, than on the placebo. Comparable figures for the left grip were 14 and 13 per cent. (all significant at the 5 per cent. level).

But there was only a slightly (non-significant) greater improvement on phenylbutazone than on oxyphenbutazone—the difference being 4 per cent. for the right grip and 1 per cent. for the left.

ASSESSMENT OF PAIN

At the end of each 3-week period, the patients recorded a subjective impression whether the degree of pain was greater, less, or the same as at the beginning of each period.

52 patients completed all three treatments, providing 104 direct comparisons between two consecutive treatments.

Phenylbutazone *v.* Placebo (35 patients).—Nineteen (54 per cent.) experienced *less* pain on phenylbutazone, six (17 per cent.) *more* pain, and ten (29 per cent.) the *same* degree of pain.

Oxyphenbutazone *v.* Placebo (34 patients).—21 (62 per cent.) experienced *less* pain on oxyphenbutazone, five (15 per cent.) *more* pain, and eight (23 per cent.) the *same* degree of pain.

Oxyphenbutazone *v.* Phenylbutazone (35 patients). Fifteen (43 per cent.) experienced *less* pain on oxyphenbutazone, thirteen (37 per cent.) *more* pain, and eight (20 per cent.) the *same* degree of pain.

To facilitate comparison, these results are assembled in Table VII. In brief, between 55 and 65 per cent. of patients had less pain on both drugs than on the placebo, but there was little difference between the percentage who felt less pain on oxyphenbutazone than on phenylbutazone (43 per cent.), and the percentage who felt the opposite (37 per cent.).

TABLE VII

DIFFERENCES (per cent.) BETWEEN EACH PAIR OF TREATMENTS AS REGARDS PATIENT'S ASSESSMENT OF "AMOUNT OF PAIN"

Difference Between		Less Pain on 1 than on 2 %	More Pain on 1 than on 2 %	No Difference %	No. of Patients
1	2				
B	P	54	17	29	35
T	P	62	15	23	34
T	B	43	37	20	35
B	Pre-trial period	78	11	11	19
T	Pre-trial period	73	7	20	15
P	Pre-trial period	33	44	22	18

78 per cent. of the nineteen who started on phenylbutazone and 73 per cent. of the fifteen who started on oxyphenbutazone, but only 33 per cent. of the eighteen who started on the placebo tablets felt less pain in this first period than before starting the course (Table VII).

ASSESSMENT OF FREEDOM OF MOVEMENT

As with pain, this also was a subjective estimate by the patient whether there was more, less, or the same freedom of movement on each type of tablet compared with the previous type (or for first tablets, compared with the pre-trial period). The results are tabulated in Table VIII.

TABLE VIII

DIFFERENCES (per cent.) BETWEEN EACH PAIR OF TREATMENTS AS REGARDS PATIENT'S ASSESSMENT OF FREEDOM OF MOVEMENT

Difference Between		More Movement on 1 than on 2 %	Less Movement on 1 than on 2 %	No Difference %	No. of Patients
1	2				
B	P	51	31	17	35
T	P	56	15	29	34
T	B	43	34	23	35
B	Pre-trial period	84	16	nil	19
T	Pre-trial period	67	7	26	15
P	Pre-trial period	28	56	17	18

Phenylbutazone *v.* Placebo (35 patients).—Of those who received phenylbutazone immediately before or after the placebo tablets, eighteen (51 per cent.) felt they had *more* freedom of movement on phenylbutazone than on the placebo, eleven (31 per cent.) *less*, and six (17 per cent.) the *same*.

Oxyphenbutazone *v.* Placebo (34 patients).—Nineteen (56 per cent.) had *more* freedom of movement on oxyphenbutazone as on the placebo, five (15 per cent.) *less*, and ten (29 per cent.) the *same*.

Oxyphenbutazone *v.* Phenylbutazone (35 patients). Fifteen (43 per cent.) had *more* freedom of movement on oxyphenbutazone than on phenylbutazone; twelve (34 per cent.) *less*, and eight (23 per cent.) the *same*.

Thus, between 50 and 60 per cent. thought that both drugs gave more freedom of movement than the placebo, but there was little difference between the percentage who considered oxyphenbutazone gave more movement than phenylbutazone (43 per cent.) and the percentage who thought the opposite (34 per cent.).

FUNCTIONAL CAPACITY

This was estimated by the physician in five grades:

(1) Fully employed or employable in normal work and able to undertake normal physical recreations.

(2) Fully employed in special work after vocational training, or doing light or part-time work in normal occupation. Limitation in the amount of physical recreation that could be taken. Housewives able to do all but the heaviest housework.

(3) Not employed or unemployable. Very limited physical activity and little or no capacity for physical recreation. Housewives able to do light housework and/or limited shopping only. In-patients in hospital for treatment, but up and about in the ward.

(4) Confined to hospital, house, or wheel-chair, but able to look after themselves in the essentials of life. In-patients in hospital for treatment sitting up, but not getting about.

(5) Confined to bed and unable to look after themselves. In-patients on complete rest in bed.

The distributions in these grades at the start of the trial of all entrants and of those who completed all three treatments (*i.e.* omitting the eight withdrawals) were:

Grade	All 60 Entrants	52 who Completed the Trial
2	37	33
3	21	18
4	2	1
Total ..	60	52

For two patients the gradings at subsequent assessments were incomplete (both were initially Grade 2) leaving fifty for comparison.

No changes of more than one grade occurred during any specified treatment. Of the fifty patients, the numbers who changed one grade up or down were:

Treatment	Improvement	Deterioration
Phenylbutazone ..	9	2
Oxyphenbutazone ..	5	2
Placebo	1	3

Of the nine who improved on phenylbutazone, two deteriorated on the placebo. One of these, initially Grade 4 (above), deteriorated to Grade 5 on placebo in the first period, improved to Grade 4 again on oxyphenbutazone in the second period, and improved still further to Grade 3 on phenylbutazone in the final period.

One patient deteriorated on phenylbutazone in the second period, but improved again on oxyphenbutazone in the third period; another patient, however, did the opposite.

Patient's Preference

At the conclusion of the trial, the patients were asked their order of preference in regard to the three types of tablets. This could not be indicated by the eight who did not complete the course, and was not recorded by two other patients. The views of the remaining fifty patients are tabulated in Table IX, where the six possible orders of preference are labelled *a* to *f*.

Table IX

PATIENT'S PREFERENCES FOR THE THREE TYPES OF TABLET

Group	Order of Preference			No. of Patients
	1	2	3	
a	B	T	P	20½*
b	B	P	T	4½*
c	T	B	P	12*
d	T	P	B	7
e	P	B	T	4
f	P	T	B	1
No preference (B = T = P)				1
Total				50
Withdrawals				8
Not Stated				2
Total No. of Patients				60

* The preference B, T = P given by one patient was allocated as ½ to (a) and ½ to (b).
The preference B = T, P given by two patients was allocated as ½ to (a) and ½ to (c).

Table IX shows that phenylbutazone was placed first by 25, oxyphenbutazone by nineteen, and the placebo by five; one patient considered all three types to be equal. This arrangement is in accordance with the results obtained from the analysis of improvement in grip.

Of the 25 who placed phenylbutazone first, twenty placed oxyphenbutazone second, and four the placebo; the remaining one considered there was no difference between oxyphenbutazone and the placebo.

Of the nineteen who placed oxyphenbutazone first, twelve placed phenylbutazone second, and seven the placebo.

Of the five who placed the placebo first, four placed phenylbutazone second.

Ignoring the placebo, 29 patients preferred phenylbutazone to oxyphenbutazone, twenty preferred oxyphenbutazone, and one considered them equal.

Discussion

This trial—in which two active drugs and a placebo were given in succession to each patient—was designed so that each treatment preceded the other treatments in an equal number of patients; and each treatment occurred with equal frequency as the first, second, and third in order.

This facilitated the application of statistical procedures whereby the residual effect of the drugs could be estimated. It is remarkable that, despite the slow excretion of the two active drugs (Burns and others, 1955a, b, reported this as "a biologic half-life of 2-3 days"), only a negligible residual effect could be demonstrated in relation either to progress or to side-effects when the treatments were changed at 3-week intervals. Because the residual effect was negligible it was permissible to compare the direct effects of the three types of tablet and this confirmed the findings of other workers that both drugs have a significant therapeutic effect. This is judged by the relative improvement in strength of grip, relief of pain, freedom of movement, and functional capacity on these drugs as compared with the placebo.

On an equivalent dosage (800 mg. per day) no statistically significant differences could be shown between phenylbutazone or oxyphenbutazone as regards any of the five assessments made. The small differences found (which could well have been chance ones) favoured oxyphenbutazone as regards

pain and freedom of movement, but as regards grip, functional capacity, and patient's preference, they tended, if anything, to favour phenylbutazone. Three of the five assessments therefore favoured the parent substance, and two favoured the derivative, which again is what one would expect if these were purely chance differences. We conclude therefore that in regard to both pain relieving properties and therapeutic potency there is little to choose between phenylbutazone and oxyphenbutazone. Thus, we were unable to confirm the impressions of Hart and Burley (1959), Mason and Cramer (1959), and others.

Furthermore, in this short-term trial, side-effects were no more frequent on phenylbutazone than on oxyphenbutazone, or indeed than on the placebo. They were reported by 28 per cent. of the patients whilst on phenylbutazone, by 31 per cent., whilst on oxyphenbutazone, and by 31 per cent. whilst on the placebo. Also the mean number of side-effects per patient on phenylbutazone was 0·34, compared with 0·38 per patient on oxyphenbutazone and 0·44 per patient on placebo. Nearly twice the number of gastro-intestinal reactions were reported on oxyphenbutazone as on phenylbutazone, and the three instances of buccal ulcer all occurred during the oxyphenbutazone period.

Our results were, however, in accordance with the findings of Mason and Cramer (1959), Graham (1960), and others, that a high proportion of patients intolerant to phenylbutazone are tolerant to oxyphenbutazone.

The incidence of side-effects on the placebo was high—31 per cent.—the same as on oxyphenbutazone. Most of these occurred when the placebo was the first treatment given, and it is remarkable that oedema of ankles occurred at least as frequently on the placebo as on the active drugs, even when it was the first treatment.

Summary

Phenylbutazone, its derivative oxyphenbutazone, and a placebo were administered in succession to sixty patients (11 males, 49 females) with rheumatoid arthritis. Their mean age was 53 years and the average duration of the disease 5 years. Each patient received each treatment for 3 weeks, and assessments were recorded of grip, degree of pain, freedom of movement, functional capacity, and side-effects. The order of administration was randomized and only the chief pharmacist knew which drug was being given at any time.

A method of analysis, designed to assess the hangover effects of the treatments, showed these to be negligible.

Results were in keeping with the findings of other workers, that phenylbutazone (Butazolidin) and oxyphenbutazone (Tanderil) are both potentially effective in the symptomatic treatment of rheumatoid arthritis, both drugs giving significantly better results than the placebo. But no significant differences could be demonstrated between phenylbutazone and oxyphenbutazone by any of the assessments made. Nor were the small differences obtained consistent. Three assessments slightly favoured phenylbutazone, and two oxyphenbutazone.

There was no significant difference between the percentage of side-effects recorded from phenylbutazone, oxyphenbutazone and the placebo; and whilst five out of six patients intolerant to phenylbutazone were tolerant to oxyphenbutazone, in two instances the converse was true.

We would express our great indebtedness to Dr. W. S. Stoddart for his assistance, not only in the preparatory stages of the trial, but at subsequent stages also, including discussions on the results.

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APPENDIX

A method described by Williams (1949) was used to estimate the *residual* effect of the preceding treatment, and to allow for that effect (if any) in comparing the *direct* effects of the three treatments—phenylbutazone, oxyphenbutazone, and placebo. The only other published trial we know of in which measurement of residual effect was attempted is that of Raymond, Lucas, Beesley, O'Connell, and Roberts (1957), who adopted the same method in a trial of six tranquillizing drugs.

The conditions essential for application of the method are that:

(1) Each treatment shall be preceded by each other treatment equally frequently;
(2) Each treatment shall occur equally frequently in each position.

As initially planned, both conditions were satisfied. There were ten patients in each of the six "order of treatment groups"—BTP, BPT, TBP, TPB, PBT, PTB (where B = phenylbutazone, T = oxyphenbutazone, and P = placebo). Oxyphenbutazone, for example, would have been preceded by phenylbutazone for twenty patients, and by the placebo for twenty patients. Also it would have been given to twenty patients in the first 3-week period, twenty in the second, and twenty in the third. The same was true of the other two treatments, and each order of treatment group would have comprised ten patients.

But because, for various reasons, eight patients did not receive all three types of tablets (see Section 6) some of the sets of ten were incomplete. The conditions (above) were then satisfied by forming seven complete sets of the six orders of treatment, taking the first seven who completed order BTP, the first seven who completed order BPT, and so on. This involved only 42 out of the 52 patients available, but as will appear later, the omission of the ten who formed incomplete sets did not prejudice the results.

Four sources of variation were taken into account:

(1) between patients
(2) between 3-week periods
(3) between the direct results of treatment
(4) between the residual effects of preceding treatment.

Following the technique set out by Williams

TABLE A

ANALYSIS OF VARIANCE PERCENTAGE IMPROVEMENT IN GRIP
Seven patients in each of six order (of treatment) groups

Percentage Improvement in Grip		Degrees of Freedom	Sum of Squares		Mean Square Adjusted	Variance Ratio (F)	*P*
			Direct Results Adjusted	Residual Effects Adjusted			
Right	Patients	41	104,879		2,558	5·94	<0·01
	Between Orders of Treatment	5		7,411	1,482	0·55*	>0·05
	Between Patients on the Same Order of Treatment	36		97,468	2,707		
	3-week Periods	2	775		387	0·90	>0·05
	Treatments:						
	Direct Results	2	5,930	6,229	2,965	6·88	<0·01
	Residual Effects	2	627	328	164	0·38	>0·05
	Error	78	33,608		431		
	Total	125	145,819				
Left	Patients	41	73,407		1,790	2·67	<0·01
	Between Orders of Treatment	5		7,394	1,479	0·81*	>0·05
	Between Patients on the Same Order of Treatment	36		66,013	1,834		
	3-week Periods	2	1,300		650	0·97	>0·05
	Treatments:						
	Direct Results	2	3,933	4,950	1,967	3·11	=0·05
	Residual Effects	2	1,089	72	36	0·06	>0·05
	Error	78	49,305		632		
	Total	125	129,054				

* Divisor = mean square for between patients in the same order of treatment.

(1949), suitable sums of squares were computed and the resulting analysis of variance for percentage improvement in right and left grip is shown in Table A.

For each grip the variation in improvement due to differences between patients was, as would be expected, significant at the 0·01 level. When this was subdivided into two parts, the mean square for the differences between the six orders of treatment was less than that between patients on the same order of treatment (within orders of treatment). Thus the amount of improvement was independent of the order in which the treatments were given.

The variation due to differences between the three 3-week periods was not significant for either grip, *i.e.* there was no secular trend such as might have arisen from natural remission of the disease.

Two sums of squares are available for differences between the direct results of the three treatments. The lesser of the two is the result when allowance has been made for the residual effect of the preceding treatment.

Similarly, two sums of squares are available for these residual effects, the lesser taking into account the direct effects. The important point is the smallness of the adjusted mean square for residual effects—not significant at the 5 per cent. or even at the 20 per cent. level—so that it can be concluded that the improvement on any of the three treatments was independent of any residual effect from preceding treatment.

The mean square for direct effects when adjusted for residual effects (such adjustment being negligible in this case) was significant at the 0·01 level for the right grip, but was just on the borderline of significance at 0·05 level for the left grip.

This analysis shows therefore that the residual effects of the preceding tablets were negligible, and that it was valid therefore to compare the direct results of the three treatments. In doing this it was no longer necessary to restrict the comparison to the 42 patients comprising seven complete sets of the six orders. All 52 patients could be included. Comparisons of the mean improvement based alternatively on 42 and 52 patients gave the following results:

Treatment	Percentage Improvement of Right and Left Grip			
	Right		Left	
	N = 42	N = 52	N = 42	N = 52
Phenylbutazone ..	24·9	27·9	23·7	22·4
Oxyphenbutazone ..	20·5	23·4	18·9	20·3
Placebo	8·3	8·4	8·7	7·9

Essai controlé de la phénylbutazone, de la oxyphenbutazone et d'un *placebo* (substance inerte) dans le traitement de l'arthrite rhumatismale

RÉSUMÉ

On a administré successivement de la phénylbutazone, son dérivé oxyphenbutazone et un *placebo* (substance-témoin inerte) à soixante malades (11 hommes, 49 femmes) atteints d'arthrite rhumatismale. L'âge moyen des malades était 53 ans et la durée moyenne de la maladie 5 ans. Chacune de ces substances était administrée à chaque malade pendant 3 semaines et on enregistrait la force de la poigne, l'intensité de la douleur, l'amplitude des mouvements, la capacité fonctionnelle et les effets secondaires. L'ordre d'administration était déterminé par le hasard; seulement le pharmacien principal connaissait l'identité de la substance employée au moment donné.

Une méthode d'analyse conçue pour évaluer les effets secondaires des traitements a montré qu'ils étaient négligeables.

Les résultats s'accordaient avec ceux obtenus par d'autres auteurs, montrant que la phénylbutazone (Butazolidin) et l'oxyphenbutazone sont potentiellement efficaces dans le traitement symptomatique de l'arthrite rheumatismale et que les deux médicaments produisent des résultats appréciablement supérieurs à ceux du *placebo*. Toutefois, aucune des méthodes d'évaluation employées n'a décélé une différence significative entre la phénylbutazone et l'oxyphenbutazone. Les faibles différences observées étaient inconséquentes. Trois évaluations favorisaient légèrement la phénylbutazone et deux autres l'oxyphenbutazone.

On n'a pas noté de différence appréciable dans la proportion des effets secondaires provoquée par la phénylbutazone, l'oxyphenbutazone et le *placebo*; tandis que cinq malades sur six qui ne toleraient pas la phénylbutazone ont accepté l'oxyphenbutazone, chez deux autres malades c'était le contraire.

Prueba controlada de la fenilbutazona, oxifenbutazona y de un *placebo* (substancia inerta) en el tratamiento de la artritis reumatoide

SUMARIO

Se administraron en sucesión fenilbutazona, su derivado oxifenbutazona y un *placebo* (substancia inerta de control) a sesenta enfermos (11 hombres, 49 mujeres) con artritis reumatoide. La edad media de los enfermos era 53 años y el término medio de duración de la enfermedad 5 años. Cada una de las diferentes substancias fué administrada a cada enfermo durante 3 semanas, y se anotaron los resultados de las investigaciones de la fuerza al asir, intensidad del dolor, libertad de movimiento, capacidad funcional y efectos secundarios. El orden de administración fué seleccionado al azar y sólo el jefe de farmacia conocía la substancia administrada en cada momento.

Un método de análisis planeado para determinar los

post-efectos de los tratamientos demostró que dichos post-efectos eran negligibles.

Los resultados fueron similares a los de otros investigadores, demonstrando que la fenilbutazona (Butazolidin) y oxifenbutazona (Tanderil) son ambas potencialmente efectivas en el tratamineto sintomático de la artritis reumatoide, produciendo ambos productos resultados significativamente superiores a los obtenidos con el *placebo*. No se apreciaron diferencias significativas entre la acción de la fenilbutazona y la de la oxifenilbutazona en ninguna de las valoraciones efectuadas. Las pequeñas diferencias halladas no fueron consistentes. Tres valoraciones favorecieron ligeramente a la fenilbutazona y dos a la oxifenbutazona.

No se apreció diferencia significativa entre el percentaje de efectos secundarios producidos por la fenilbutazona, oxifenbutazona y el *placebo*; y mientras que cinco de los seis enfermos que no toleraron la fenilbutazona, aceptaron oxifenbutazona, en dos casos lo sucedió lo contrario.

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COMBINED ASPIRIN AND CORTISONE TREATMENT OF ACUTE RHEUMATIC FEVER

A CONTROLLED TRIAL IN YOUNG MEN

BY

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For many years large doses of salicylate have been used in the treatment of acute rheumatic fever (Coburn, 1936, 1943; Manchester, 1946). Although the acute manifestations of the disease are partially suppressed (Illingworth, Burke, Doxiadis, Lorber, Philpott, and Stone, 1954), there is no convincing evidence that chronic damage to the heart is prevented (Bywaters, 1950).

However, the introduction of the adrenocortical hormones in 1948 brought hope of a more radical form of treatment (Hench, Kendall, Slocumb, and Polley, 1949). Anecdotal studies have emphasized the value of steroid therapy in acute rheumatic fever (Massell, 1954; Debré, Mozziconacci, and Caramanian, 1955), and there is evidence that carditis is less likely to develop if large doses of cortisone are given at an early enough stage in the disease (Roy and Massell, 1956). Nevertheless, two well-controlled therapeutic trials comparing the effects of aspirin, cortisone, and adreno-corticotrophic hormone in children (M.R.C. and A.H.A., 1955) and in American airmen (Houser, Clark, and Stolzer, 1954) have shown that *when used singly* each of these drugs has a similar effect on the course of the acute disease. These trials have not, however, assessed the effect of cortisone, because there were no untreated controls and no patients treated with both aspirin and steroids.

The present paper describes a controlled therapeutic trial in 28 young men designed to assess the response to cortisone. The course of acute rheumatic fever was followed when using high doses of salicylate, either alone or combined with cortisone.

Methods

In the British Army many patients with doubtful or mild rheumatic fever are admitted to hospital so that the diagnostic criteria laid down by Duckett Jones (1944) have been modified and made more rigid. These are described in detail elsewhere (Slater and Rosenbaum, 1959), but are similar to the criteria used by Houser and others (1954) and in the M.R.C. and A.H.A. Trial (1955). All soldiers with suspected acute rheumatic fever in the Aldershot area between June, 1955, and June, 1956, were seen personally and assessed for entry to the trial. No case which satisfied the diagnostic criteria was excluded. The treatment to be given was determined at random by the toss of a coin.

Aspirin.—This was given in five separate doses totalling 1 to 1½ gr. per lb. body weight per day. The exact amount was governed by the development of tinnitus and slight deafness. Blood salicylate levels were estimated 2 hours after the morning dose once weekly and with few exceptions were always above 30 mg. per 100 ml.

Cortisone.—This was given by mouth in the following doses: 300 mg. per day on the first day; 200 mg. per day on the second, third, and fourth days; 100 mg. per day for the remainder of the first 3 weeks; 50 mg. per day thereafter, unless treatment had already been stopped.

Except for the addition of cortisone to the members of one group, the therapy in each case was identical. Salt intake was restricted to less than 1 g. NaCl per day and extra potassium (76 mEq/day) was given as the citrate. Intramuscular penicillin was given for 10 days from the day of entry to the trial and thereafter oral sulphadimidine 1 g. daily. A strict and standard regime for mobilizing the patient was used. Usually this took about 4 weeks. Drug treatment was continued until full clinical recovery *and* until three consecutive erythrocyte sedimentation rate estimations (Westergren) were below 10 mm./hr. These were performed at 4-day intervals after the first normal reading. The patient was not allowed to begin getting up unless the erythrocyte sedimentation rate was normal on the fourth and eighth days after stopping drug treatment.

Assessment of progress was made at standard times on specially-prepared charts. Entries were made at least every morning until the patient began to get up, and at weekly intervals thereafter. Apical systolic murmurs were recorded by a modified version of Levine's grading (Levine and Harvey, 1949), the length of the murmur also being noted. Apical and basal diastolic murmurs were listened for in the appropriate positions with the bell and diaphragm of the stethoscope respectively. The pulse rate and oral temperature were recorded 4-hrly when the patient was febrile and otherwise 12-hrly. The pulse rate during sleep was taken nightly at 2 a.m. An erythrocyte sedimentation rate, chest radiograph (by a standard technique), and total white blood cell count were recorded weekly unless otherwise stated. After admission to the trial, 12-lead electrocardiographic tracings were taken on alternate days for 8 days and then at weekly intervals until two consecutive tracings were normal.

Results

Table I shows that the main clinical features of the disease at the time of entry to the trial were comparable. On the day that therapy was begun, an equal proportion of patients in each group had evidence of cardiac involvement, the extracardiac manifestations of the disease were similar in degree, in all patients treatment was begun less than 10 days from the onset of symptoms, and equal numbers had had a previous attack. The patients receiving aspirin and cortisone were on the whole slightly younger than those given aspirin alone.

The response to treatment of specified features of the disease is shown in Table II, and the Figure (opposite).

TABLE I

SPECIFIC CLINICAL FEATURES AT THE BEGINNING OF TREATMENT

Clinical Features		Group			
		Aspirin Alone (15 Cases)		Cortisone and Aspirin (13 Cases)	
		Range	Mean	Range	Mean
Age (yrs)		18–24	20·3	17–21	18·8
Duration of Symptoms (days)		1–7	3·8	1–8	4·3
Temperature (° F.)		99·8–101·8	100·6	99·4–103·0	100·9
Erythrocyte Sedimentation Rate (mm./hr)		34–110	64·2	20–115	64·0
Pulse Rate during Sleep		60–98	75·3	68–96	79·5
Number of Inflamed Joints		1–8	2·8	1–5	2·4
Number of Patients with	Abnormal Heart Murmurs	1		1	
	Past Rheumatic Fever	4		4	
	Preceding Sore Throat	11		7	
	Prolonged P–R Interval	4		4	
	Leucocytosis	4		4	

TABLE II

RESPONSE TO TREATMENT

Duration of Symptoms and Therapy	Group			
	Aspirin Alone (15 Cases)		Cortisone and Aspirin (13 Cases)	
	Mean	Range	Mean	Range
Fever (hrs)	35·7	12–88	9·3	4–12
Inflamed Joints (days)	3·67	2–6	1·8	1–3
Raised Erythrocyte Sedimentation Rate (days to first normal reading)	22·1	15–43	17·5	7–29
Drug Therapy (days)	33·8	22–52	37·6	24–44
Complete Rest in Bed (days)	47·8	23–87	46·5	34–91

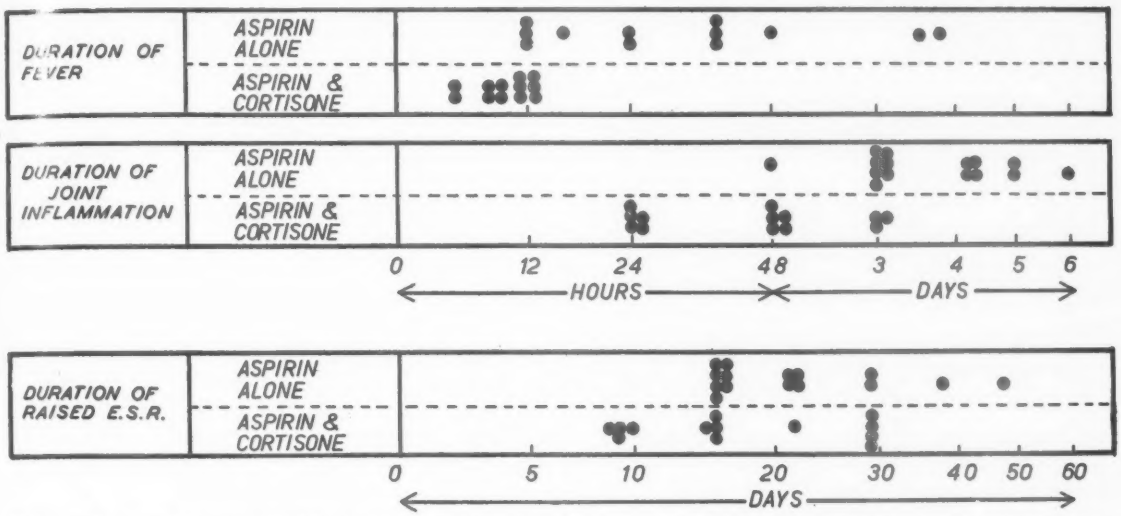

Figure.—Response to treatment of fever and joint inflammation in 6 days, and of raised erythrocyte sedimentation rate in 60 days.

The duration of fever and painful joints was shortened by giving cortisone as well as aspirin. No patient receiving cortisone had fever for longer than 12 hours from the time that therapy was started compared with nine out of twelve patients on aspirin alone. Conversely, six out of eleven patients on the combined therapy had lost their fever in less than 12 hours whereas none of the patients on aspirin alone did so. Ten out of thirteen patients receiving cortisone had painless joints within 72 hours of starting treatment, but only one of those on aspirin alone was free of joint symptoms within this time; in contrast it took 4 to 6 days for joint symptoms to subside in seven out of the fifteen patients on aspirin alone, whereas all the patients on the combined therapy were symptom-free in 3 days or less. Despite the small numbers, these differences are considerable, consistent, and highly significant statistically.

In addition, the duration of a raised erythrocyte sedimentation rate (time to first normal reading) was shortened by giving cortisone; three patients had normal values at 8 days compared with none in the aspirin group. The erythrocyte sedimentation rate also fell more rapidly in the patients on the combined therapy (Table III). Taking mean

TABLE III

ERYTHROCYTE SEDIMENTATION RATE (mm./hr) AT SPECIFIED TIMES

Erythrocyte Sedimentation Rate		Aspirin Alone (15 Cases)			Cortisone and Aspirin (12 Cases)†		
		Mean	Range		Mean	Range	
During Treatment	Initial reading ..	64·0 (100%)	34–110		64·2 (100%)	20–115	
	Fall 1st to 8th day ..	27·3 (58%)	0–70		38·2 (40%)	0–82	
	Fall 1st to 15th day ..	32·0 (50%)	0–102		58·0 (9·7%)	16–95	
After Stopping Treatment	1st day	5·0	2–9	* 0	4·1	2–6	* 0
	4th day	4·8	2–12	1	10·2	2–26	5
	8th day	5·1	2–18	2	11·0	3–20	4
	15th day	4·0	1–14	1	9·7	2–25	4
	22nd day	3·9	1–10	0	7·2	2–30	2
	29th day	4·5	2–9	0	5·7	2–12	1

* Number of patients with an abnormal erythrocyte sedimentation rate.
† Excluding one patient whose sedimentation rate remained elevated until a septic tooth was extracted.

values, the sedimentation rate at 15 days had fallen to 50 per cent. of the initial reading in patients given aspirin alone compared with 10 per cent. in patients on the combined treatment.

Two patients in each treatment group developed new abnormal murmurs in the heart. The duration of a prolonged P-R interval on the electrocardiogram was 6, 10, and 40 days for three patients treated with aspirin alone, and 11, 13, 15, and 143 days in four patients receiving the combined therapy. Changes in pulse rate were not analysed because, after the temperature became normal, the pulse rate was below 90 per min. in every case. Two patients on the combined treatment developed bradycardia with ventricular rates of below 50 per minute.

Table III shows that after the withdrawal of drug treatment there was a transient rise in the erythrocyte sedimentation rate in the patients receiving the combined treatment. This happened without clinical evidence of renewed rheumatic activity or change in the heart rate, except that one man had a mild recurrence of joint symptoms with fever on the fourth day after treatment was discontinued. Another patient treated with aspirin alone experienced a similar mild relapse on the 24th day after drug treatment was discontinued. Although not satisfying the requisite diagnostic criteria, both these events were regarded as mild recurrences of rheumatic activity and treatment was restarted. Chiefly because of this rebound rise in erythrocyte sedimentation rate, the mean length of drug therapy and of complete rest in bed was similar in both groups.

Both aspirin and cortisone were well tolerated, except by one man who developed vomiting, overbreathing, and mental disorientation after one week's treatment with aspirin alone. Cortisone did not cause any definite toxic effects but produced a more rapid gain in weight. After 2 weeks' treatment patients receiving cortisone had gained a mean of 5 kg. compared with 0·5 kg. in the aspirin group. Whatever the treatment, most patients developed mild mooning of the face and acne became worse. No specific record of these changes was kept because they were so slight and could hardly be measured.

Discussion

The results of this controlled study show that the fever and joint inflammation of acute rheumatic fever in young men can be alleviated more rapidly by giving cortisone together with large doses of aspirin than by giving aspirin alone. Also the erythrocyte sedimentation rate fell to normal more rapidly but there was a transient rise when treatment was stopped. Owing to the design of the trial this meant that the length of drug treatment and the time spent in bed were similar in each group. There were probably too few cardiac manifestations to justify comment, but the addition of cortisone did not seem to influence the duration of a prolonged P-R interval.

Although the numbers are small these results would appear valid because the patients formed an unusually homogeneous group and were observed personally under uniform conditions. Unlike other larger trials, there was no loss of information from grouping together dissimilar cases or from the use of case notes instead of seeing the patients personally.

Because cortisone shortens the duration of the extracardiac manifestations of acute rheumatic fever, it does not follow that subsequent chronic heart disease will be lessened. This is a difficult question which will take decades to answer. But, assuming that there is some parallel between joint inflammation and cardiac inflammation, it seems unlikely that the more rapid relief of one will not be accompanied by some amelioration in the other. The careful and fully-controlled studies of Illingworth, Lorber, Holt, and Rendle-Short (1957) have shown that, in children with acute rheumatic fever, cortisone gives better results than aspirin, and that cortisone with combined aspirin is better than cortisone alone. Not only were the acute manifestations reduced more rapidly, but fewer heart murmurs were present one year later in the cortisone-treated patients. Superficially, the disappointing results of the Anglo-American trial (1955) and the trial by Houser and others (1954) appear to differ from the findings of Illingworth and his co-workers. Both studies compared the relative effects of orally-administered aspirin with intramuscular injections of cortisone. For the first 7 days of therapy more patients receiving cortisone had fever and joint involvement, but this is probably explained by the slow absorption of intramuscular cortisone which may also cause local inflammation. Thereafter these manifestations were less frequent in the hormone-treated cases, but there was a greater tendency for them to reappear at the end of treatment. The signs of carditis were also little influenced by the form of treatment although soft apical systolic murmurs and nodules disappeared more rapidly in the group receiving cortisone.

In diseases which cause long-term disability, therapeutic trials which show equal effects with different drugs during the acute phase are difficult

to interpret. Assuming that drug treatment is better than no treatment, useful conclusions depend largely on how the drugs produce their beneficial effects. Although aspirin may have some specific anti-inflammatory effect in rheumatic fever, it also has a powerful non-specific analgesic and antipyrexial action. Refined techniques (Peterson, Black, and Bunim, 1958) have shown that salicylate does not stimulate adrenocortical function. Cortisone, however, is a well-known anti-inflammatory agent and it is unlikely that it would relieve the acute manifestations of rheumatic fever other than by suppressing the inflammatory process. Therefore, apart from the question of toxicity, to show that cortisone is as effective as aspirin in relieving the acute manifestations of rheumatic fever could reasonably be interpreted as indicating that cortisone is the better form of treatment.

Both the present study and the two trials described above show that the erythrocyte sedimentation rate falls to normal more rapidly when rheumatic fever is treated with cortisone. In the other trials treatment was stopped after 6 weeks irrespective of the progress of the patient, following which there was a recrudescence of rheumatic activity and a "rebound" rise in the erythrocyte sedimentation rate in a greater proportion of hormone-treated subjects. In the present study, treatment was continued until, by pre-arranged criteria, the disease was judged to be quiescent. Nevertheless, a small transient rise in the erythrocyte sedimentation rate was seen in the patients who had been given cortisone. In the absence of other signs of continuing rheumatic activity, this may be a non-specific response to a sharp fall in the steroid dose. For example, Robinson, Wolfson, and Duff (1951) found that, in patients with eye disease who were treated with corticotrophin, an initially normal erythrocyte sedimentation rate rose to high levels when the steroid dose was suddenly reduced. However, since our ability to detect continuing mild rheumatic activity is clearly limited, a definite rise in the erythrocyte sedimentation rate to abnormal levels after stopping steroid therapy (especially if the dose has been reduced gradually) should be viewed with concern even in the absence of other signs of the disease.

This small study gives support from a different age-group to the conclusions reached by Illingworth and others (1957) on the benefits of adrenocortical steroid therapy in acute rheumatic fever as seen in children.

Until evidence on the state of the heart in later life becomes available, it would seem rational to recommend cortisone or an appropriate analogue in the treatment of acute rheumatic fever in patients of all ages.

Summary

A controlled therapeutic trial of the value of cortisone in the treatment of acute rheumatic fever in young adults is described.

28 patients were randomly divided into two treatment groups. High doses of aspirin were used and therapy was identical except for the addition of cortisone to one group.

The duration of fever, joint involvement, and raised erythrocyte sedimentation rate was considerably reduced by giving cortisone in addition to aspirin.

I am grateful to Dr. J. H. Edwards for much constructive criticism, and to Drs. G. S. Wakefield and D. Beavan for their co-operation with some of the cases. I am also indebted to the Army Medical Authorities, whose interest made this work possible.

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Traitement combiné du rhumatisme articulaire aigu par l'aspirine et la cortisone

RÉSUMÉ

On décrit un essai contrôlé de la cortisone dans le traitement du rhumatisme articulaire aigu chez les jeunes adultes.

Vingt-huit malades furent répartis au hasard entre deux groupes de traitement. On employa des doses fortes d'aspirine, les mêmes pour les deux groupes, mais un de ces groupes reçut de la cortisone en plus.

La durée de la fièvre, la sévérité de l'atteinte articulaire et la vitesse de sédimentation globulaire accusèrent une diminution considérable chez ceux qui reçurent de la cortisone en plus de l'aspirine.

Tratamiento combinado del reumatismo poliarticular agudo con aspirina y cortisona

SUMARIO

Se describe una prueba controlada del valor de la cortisona en el tratamiento de la poliartritis articular aguda en adultos jóvenes.

28 enfermos fueron divididos al azar en dos grupos de tratamiento. Se emplearon altas dosis de aspirina, iguales en ambos grupos, pero uno de tales grupos recibió cortisona además de la aspirina.

La duración de la fiebre, afectación articular y velocidad de sedimentación eritrocitaria se redujeron considerablemente cuando se administró cortisona además de aspirina.

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PLACEBO RESPONSES IN AN ARTHRITIS TRIAL

BY

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Since the publication in this Journal of a description of the effects of placebos in rheumatoid conditions (Traut and Passerelli, 1957), there has been a growing literature on the subject of placebo responses, but little has appeared in print regarding such effects in arthritis.

During a recent intra-articular injection trial in which two steroid preparations and a placebo were compared, it became apparent that responses to the latter were frequent and well marked. It was decided, therefore, to make a parallel study of the whole question of placebo responses as these occurred during the trial.

The results of injection of the two steroids have already been reported; one paper dealt with the effects on rheumatoid arthritics (Chandler, Wright, and Hartfall, 1958) and the other with the effects on osteo-arthritics (Wright, Chandler, Morison, and Hartfall, 1960).

The present paper is concerned chiefly with a detailed examination of the responses to the placebo injections in the same trial. It also reports the results of a subsequent dummy tablet trial on the same group of patients. Finally, some of the implications of these findings as they apply to clinical trials are discussed.

Material

49 patients were included in the original trial, and of these, 10 dropped out for various reasons during the 18 months that the trial was in progress. The remaining 39 patients from whom results were complete, comprised 34 females and 5 males; 21 were osteo-arthritics, and the remaining eighteen rheumatoid arthritics, the knees being involved in every case. The age range was 29 to 76 years (mean 58·6). The two steroids used were hydrocortisone acetate, and hydrocortisone *tertiary* butyl acetate. The placebo consisted of the inert aqueous vehicle.

Design of Injection Trial

Every patient received three courses of injections into the affected knee, each course comprising four injections with an interval of 2 weeks between injections. There was a resting period of 2 months between courses, and the order in which courses were given was arranged so that every patient eventually received a course of each steroid and a course of the placebo.

Assessments for local pain and tenderness, range of joint movement, and walking time, were carried out at each visit. After careful consideration it was felt that walking-times would give the most useful single objective measurement by which clinical improvement or deterioration could be assessed. Patients were asked to walk a distance of 75 yards as quickly as possible while being timed by a stop-watch. The value taken was the mean of the four walking times which were measured fortnightly during the 2-month resting period following each complete injection course. These values were then expressed as percentages of the original walking time.

Alterations of less than ± 10 per cent. were classified as "unchanged", while decreases or increases of more than 10 per cent. were classified as "improvement" or "deterioration" respectively. Throughout this article the values of these walking times are referred to as "findings".

Patients were given two opportunities to express their opinion as to the value of the three injection courses. The first occasion was at the time of taking the psychological history, *i.e.* within a few weeks of completing all three courses. They were questioned again some 6 months later at the time of the second psychological interview so that the consistency of their replies was ascertained.

The patients' answers were recorded under the heading of "claims", and classified as "unchanged",

"improved", and "deteriorated". In all cases in which a patient's two replies showed inconsistency, the result was entered as "unchanged".

Results of Injection Trial

While it was found that there were more placebo responses amongst rheumatoid arthritics than amongst osteo-arthritics, this difference was not statistically significant and therefore both groups are considered together in this study. Furthermore, as the two forms of hydrocortisone injected showed no significant difference in their effects on the walking time, they have been taken together and the mean values recorded, and these results have been compared with those from injections of "placebo". Thus there were 78 courses of steroid injections and 39 courses of placebo injections, a total of 117 courses, comprising 468 actual injections.

Comparison between Steroid and Placebo Injections. Table I shows these results and, as there were two steroid courses and only one placebo course for each patient, the percentages are given in brackets for comparison. It should be noted that findings and claims do not necessarily refer to the same actual patients. For example, in line 1 (col. 4) of the Table, seven patients were found to have improved with placebo injections, but these seven did not all come from the sixteen shown in line 1 (col. 2) as claiming improvement. The same holds good for the deteriorations, in which many claims were not substantiated by findings, and conversely several who were found to have deteriorated stated that they were unchanged, and one patient actually claimed improvement. In this respect it should be pointed out that factors other than walking time might well have affected patients and so influenced their claims.

It will be seen that deteriorations are of a similar order throughout. Claims for improvement show 53 per cent. for steroids and 41 per cent. for placebo; actual findings for improvement, however, rate 25 per cent. for steroids and 18 per cent. for placebo. Although both claims and findings show higher percentages for steroids than placebo, these differences do not attain statistical significance in this relatively small sample.

TABLE I

COMPARISON OF CLAIMS AND FINDINGS WITH STEROID AND PLACEBO INJECTIONS

Result	Claims		Findings	
	Steroids (Mean of 2)	Placebo	Steroids (Mean of 2)	Placebo
Improved ..	20·5 (53%)	16 (41%)	9·5 (25%)	7 (18%)
Deteriorated ..	4 (10%)	3 (8%)	2·5 (6%)	2 (5%)
Unchanged ..	14·5 (37%)	20 (51%)	27 (69%)	30 (77%)
Total ..	39 (100%)	39 (100%)	39 (100%)	39 (100%)

$\chi^2 = 1{\cdot}57;\ 0{\cdot}5 > P > 0{\cdot}3$ $\chi^2 = 0{\cdot}6;\ 0{\cdot}8 > P > 0{\cdot}7$

Effect of Order of Courses.—It has been claimed by Fearnley, Lackner, Meanock, and Bywaters (1956) that the *order* in which courses are given has a direct bearing on the results. Using hydrocortisone and procaine courses in a controlled intra-articular trial, these workers found that on objective assessment the *first* course conferred greater benefit irrespective of the nature of the substance injected. Some evidence in support of this principle may be adduced from our results below.

Fig. 1 (opposite) shows both claims and findings with the number of improvements and deteriorations for each course. Throughout this histogram steroid and placebo results are summated, as it is only the *order* of the courses that is under consideration. In Fig. 1A it will be seen that the number of claims stating that patients were unchanged remains almost constant (16:16:17), while the claims for improvement for the second and third courses does not differ greatly from those for the first course (21:17:19). With regard to claims for deterioration, these total only eleven for all three courses, those for the second course being highest (2:6:3).

Fig. 1B deals with actual findings, and it is here that our results support the work of Fearnley and others (1956). The histogram shows that the number of patients remaining unchanged is almost twice as high for the second and third courses as for the first course (17:32:32). The number of objective improvements, however, following the first course far exceeds the sum of the improvements for the second and third courses together (19:4:5). The number of deteriorations remains almost constant at a low figure (2:3:2). It is interesting to note that while the *findings* for improvement following the first course almost equal the claims (20:21), there is no such corresponding agreement between the claims and the findings of improvement for the second and third courses. These discrepancies will be referred to in the Discussion.

Design of Tablet Trial

By the time all patients had completed their three injection courses many of the foregoing results had come to light, and it was thought that a further trial using placebo tablets only might serve to

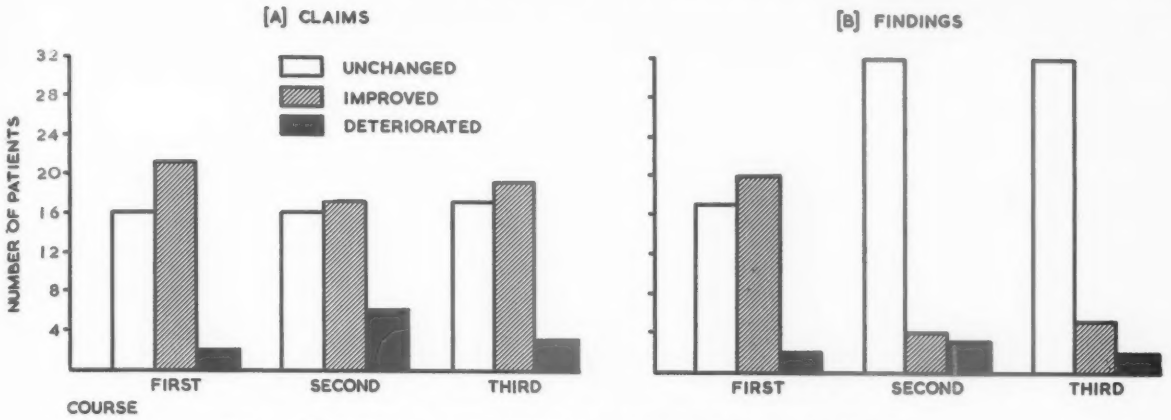

Fig. 1.—Effect of order of courses—steroids and placebos taken together in each case.

elucidate certain aspects of the problem. Two particular points on which further information was sought were whether placebo responses were consistently produced by certain patients, and whether these patients had any marked psychological characteristics.

All patients were given a week's supply of dummy tablets which contained starch, chalk, and a trace of sodium sulphate to give some taste. The tablets were issued on a normal hospital prescription and obtained from the dispensary in the usual manner. The instructions were simply "one three times daily after meals".

Patients were asked to return a form on completion of the week's course, on which they were asked to mark whether the tablets had in their opinion produced improvement, no change, or a deterioration of their condition. In addition, they were asked to note on the obverse, " . . . any other effects caused by the tablets (*i.e.* giddiness, sickness, tinglings, etc.)". One patient failed to complete the tablet trial, leaving 38 for whom results are available.

Results of Tablet Trial

Ten patients claimed improvement with dummy tablets, twelve claimed deterioration, and sixteen indicated that they were unchanged. With regard to reports on side-effects, many went far beyond any suggestions made on the form, claiming such things as headaches, impaired vision, burning sensations, and backache. One patient stated: "These tablets made my head fuzzy . . . and my tongue black". Altogether sixteen patients reported side-effects (42 per cent.).

Combined Results of the Two Trials

Table II sets out the combined results of the two trials in so far as placebo substances are concerned (the results of steroid therapy in the injection trial have been shown in Table I). It will be seen that there are more improvements after placebo injections than after placebo tablets. These results are in keeping with work by others in this field (Traut and Passerelli, 1957), who found that more than half the patients who were resistant to placebo tablets, responded to placebo injections. We also found that while only three claims of deterioration were made against placebo injections, there were twelve claims of deterioration against the tablets. This difference may be due to the method by which the placebo is given (*i.e.* injection as opposed to oral administration), and it is significant at the 3 per cent. level.

TABLE II
COMBINED RESULTS OF TRIALS 1 AND 2

Patients' Claims	Placebo Injections	Placebo Tablets
Better	16 (41%)	10 (26%)
Worse	3 (8%)	12 (32%)
Unchanged	20 (51%)	16 (42%)
Total	39 (100%)	38 (100%)

Difference in regard to worse patients is significant (Critical Ratio = 2·22 $P = 0{\cdot}03$)

We come now to the interesting relationship between placebo-response and claims of side-effects with the dummy tablets. All sixteen patients who claimed side-effects from the inert tablets either showed placebo response in the tablet trial, or had previously shown placebo response in the injection trial. Not one of the eleven patients who were

consistent non-responders in both trials reported side-effects with the dummy tablets. This finding, which is highly significant ($P < 0{\cdot}01$), is shown in Table III.

TABLE III

RELATIONSHIP BETWEEN PLACEBO RESPONDERS AND SIDE-EFFECTS

Category	Total	No. Showing Side-Effects
Placebo Responders in One or Both Trials	27	16
Constant Non-responders	11	0

$\chi^2 = 6{\cdot}65$; $P < 0{\cdot}01$

Consistency of Placebo Responses.—The degree of consistency may be judged from the fact that, dealing with placebo injections and tablets, there was one patient who claimed to be worse in both trials, four claimed to be better in both, and eleven consistently stated that they were unchanged. The remaining 22 patients were inconsistent in their placebo claims.

Of the eighteen who showed placebo-response in the injection trial, twelve continued to show such response to placebo tablets. The 27 patients shown in Table III as placebo-responders in one or both trials constitute 71 per cent. of the total.

Relationship between Frequency of Claims and Side-Effects.—It will be recalled that patients could make one claim for improvement or deterioration with each of the three injection courses, and one further such claim for the course of placebo tablets. Thus we have four occasions on which the patient either claimed or did not claim. It should be noted that all claims for improvement or deterioration with steroids or placebo are included.

It was found that no patient making less than two claims reported side-effects with placebo tablets, and it can be seen from the histogram in Fig. 2 that there were nine such cases (three made no claim and six made only one claim). Of the twelve patients who made two claims, three reported side-effects. When three claims were made, eight out of ten patients reported side-effects. Finally, in the group making the maximum of four claims, five out of seven reported side-effects with dummy tablets. Thus it appears from Fig. 2 that the frequency of claims follows closely the curve of normal distribution. Side-effects do not occur at all in the first two groups, and only to the extent of 25 per cent. in the middle group, but the frequency is much higher (70-80 per cent.) in the remaining two groups.

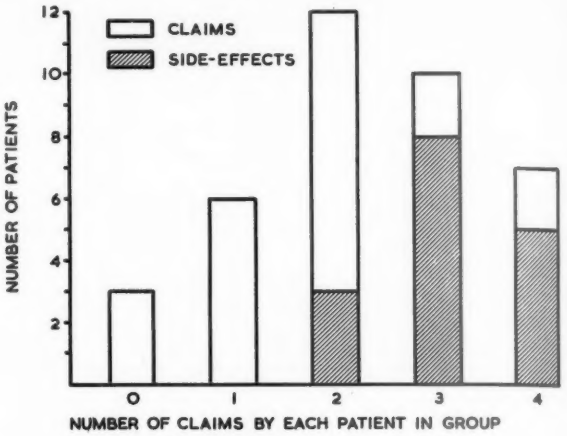

Fig. 2.—Relationship of claims to side-effects.

Psychological Investigations

A considerable part of our investigations into placebo responses was concerned with the psychological aspects of the problem. Although the bulk of these findings will form the basis of a further paper, some of the more important results will now be considered briefly.

Every patient was given two separate psychological interviews during which a special history was taken with regard to emotional stress as an aetiological factor in the arthritis.

Factors such as stress, bereavement, and marital separation were considered in so far as their occurrence coincided with the time of onset. It was found that such psychological stress occurred three times more often in the group of placebo responders than it did in those who were consistent non-responders. This finding was significant at the 2 per cent. level.

All patients were given questionnaires to complete at each of their two interviews. The first of these was the Maudsley Personality Inventory (M.P.I.), which was subsequently scored for neuroticism (higher scores indicating neurotic tendencies). The M.P.I. was also scored on the extroversion/introversion scale (low scores indicating introversion, high scores extroversion). It was found that patients claiming improvement with placebos (positive responders), showed a significant trend towards introversion ($P < 0{\cdot}03$) and a highly significant degree of neuroticism ($P < 0{\cdot}01$).

The other questionnaire, the Bernreuter Personality Inventory, confirmed many of these findings and also gave a score for social dominance. It was found that patients claiming deterioration with placebos (negative responders) scored significantly higher on the scale of social dominance, as com-

pared with those claiming improvement or reporting no change ($P < 0{\cdot}05$).

These findings are summarized in Table IV.

TABLE IV

SUMMARY OF PSYCHOLOGICAL FINDINGS

Category	Psychological Characteristics	Significance
All Placebo Responders	Major psychological stress in relation to aetiology	$P<0{\cdot}02$
	Tendency to report side-effects	$P<0{\cdot}01$
Positive Placebo Responders	Introversion	$P<0{\cdot}03$
	Neuroticism	$P<0{\cdot}01$
Negative Placebo Responders	Social Dominance	$P<0{\cdot}05$

Discussion

In recent years many placebo trials have been carried out on groups of healthy subjects, such as nurses and students, by different teams of workers in Great Britain, *e.g.* Joyce (1959) and Knowles and Lucas (1960). Their publications, together with the review of the literature by Trouton (1957), provide a useful background to placebo studies.

In America, the work of Wolf and Pinsky (1954) and of Lasagna, Mosteller, von Felsinger, and Beecher (1954), with that of Beecher (1955), drew attention to the importance of placebos and their side-effects. The excellent historical review by Shapiro (1960) gives some idea of how placebo effects have dominated therapeutics since antiquity, and yet until the fifth decade of this century only sporadic publications on the subject have appeared. The urgent necessity for further work on this subject has been emphasized by a recent annotation in the *British Medical Journal* (1961).

In the present paper, reference to Table I shows that the percentage claims for deterioration are almost the same after the placebo injections as after steroids (8 as opposed to 10 per cent.). Similarly, with the findings in which 5 per cent. show actual deterioration after placebo and 6 per cent. after steroids. The difference is negligible and suggests that such deteriorations may be due in part to natural exacerbations of the disease, rather than to the steroid injections. It has been shown, however, that repeated injections of steroids into rheumatoid arthritic knee joints cause significant radiological deterioration (Chandler and Wright, 1958). One must also make due allowances for natural remissions when considering the claims for improvement, although such cannot be specified exactly. In any case the 53 per cent. improvement claim after steroid injections is hardly impressive in view of the 41 per cent. improvement claim after placebo injections.

Perhaps more surprising are the actual findings (Table I, cols 3 and 4), which show that the percentage of objective improvement after placebo injections amounts to nearly three-quarters of that after steroids. It would appear from this finding that, with repeated intra-articular injections of steroids, much of the reputed therapeutic benefit is in fact placebo effect. The only significant difference between steroid and placebo in the entire trial was the transient improvement in relief of pain 2 weeks after one of the steroid preparations which has already been reported (Wright and others, 1960).

In the section dealing with the order of courses it was noted that the number of improvement *claims* varied only slightly between the three courses (Fig. 1A). In contrast, the objective findings (Fig. 1B) show a remarkable drop in the number of improvements following the second and third courses, as compared with those following the first course. This suggests that the enthusiasm which develops amongst the staff at the outset of any new trial is subtly but effectively communicated to the patients, and this optimism is liable to give rise to marked placebo effects. The extravagant claims so frequently made for new drugs which later prove of little value is due in part to failure to allow for this enhanced placebo effect. It would, therefore, appear highly desirable in future to conduct controlled trials in two or more phases, and to regard the results of the first phase as tentative and awaiting confirmation.

In the comparison between the injection trial and the tablet trial, we are inclined to think that the ratio of 3:2 which favours improvements with injections, and the more striking fact that four times as many patients claim deterioration with tablets, are due to the different methods of administrating the placebos. In the case of the injection courses, the whole paraphernalia of the aseptic ritual can hardly fail to impress suggestable patients, whereas the mere prescribing of tablets is surrounded by no such aura.

Joyce's view that placebo responders and non-responders form a continuum is amply borne out by our findings on the distribution of claims. The curve is that of normal frequency distribution slightly skewed to the right. The constant non-responders fall to the left and show no side-effects. The largest group are centrally placed and may be termed occasional responders who sometimes show side-effects. To the right of the curve lie the regular responders who nearly all show side-effects. It

would appear that while accurate prediction of placebo responders is not possible, the general distribution can be forecast, and in our group it was as follows: 29 per cent. non-responders, 37 per cent. occasional responders, and 34 per cent. regular responders.

In the psychological approach made in this study the findings in respect of association of stress with the onset of the disease were not unexpected in view of previous published work on this subject, *e.g.* Johnson, Shapiro, and Alexander (1947) and Hartfall (1954). The idea that placebo responders are hysterical types is not substantiated by the facts, otherwise those showing the combination of neuroticism with extroversion would be placebo responders, whereas the responders were in fact mostly neurotic introverts. It should be noted that the word neurotic in this sense refers to the trait as measured on the Maudsley Personality Inventory scale which Eysenck (1959) equates with autonomic lability. It does not necessarily indicate that such patients require psychiatric treatment.

In concluding this contribution to a difficult subject, we would emphasize that the foregoing study is based on observations made during an actual clinical trial, and as the reactions of patients suffering from a chronic disease are likely to differ considerably from those of healthy young normal subjects, this detailed report should be of interest to those engaged in planning future trials. The famous witticism uttered by Trousseau in 1833, that you should treat as many patients as possible with new drugs while they have the power to heal, is still applicable to the field of therapeutics. Indeed, it is likely to remain so, as it appears that placebo responders, like the poor, are with us always.

Summary

An injection trial, using two steroid drugs and a placebo, was carried out on a group of 39 patients, all of whom had rheumatoid or osteo-arthritis affecting the knees. This paper analyses the results of the placebo injections, together with those of a further trial, using orally-administered placebo tablets. 25 per cent. showed objective improvement with steroid injections and 18 per cent. with placebo injections, a difference which is not statistically significant with small numbers.

The order in which injection courses were given was found to have a marked effect on the results, the first course producing far greater objective improvement than either of the subsequent courses irrespective of the substance administered.

In the tablet trial, fewer claimed improvement with placebo, and more claimed deterioration than in the injection trial. The discrepancies between claims for dummy tablets and placebo injections are discussed. Altogether 71 per cent. of the patients showed a placebo response of some kind.

Placebo responders were found to show higher scores for neuroticism and introversion. Negative responders showed higher scores for social dominance. It is shown that placebo responders form a continuum coincident with a curve of normal distribution, and constant non-responders do not show side-effects. A suggestion is made regarding the conduct of clinical trials.

We are much indebted to Prof. S. J. Hartfall for his continued interest and encouragement in this work. We should also like to express our thanks to Prof. G. R. Hargreaves for allowing one of us (A.J.Y.), to devote considerable time to the psychological aspects of this study.

Finally, we wish to thank Sister P. R. Benson and her nursing staff for their co-operation.

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Réactions aux *placebos* (produits factices, témoins) dans un essai thérapeutique de l'arthrite

RÉSUMÉ

Un essai thérapeutique, en usant deux substances stéroïdes et un *placebo* en injections, fut effectué chez 39 malades atteints d'arthrite rhumatismale ou d'ostéo-arthrite avec implication du genou. Dans ce travail, on analyse les résultats obtenus avec des injections de *placebo*, ainsi que les résultats obtenus dans un autre travail, où la substance factice fut administrée sous forme de comprimés. Vingt-cinq pour cent des malades

accusèrent une amélioration objective après des injections des stéroïdes et 18% d'entre eux furent améliorés après des injections de *placebo*; cette différence, le groupe étant petit, est statistiquement insignifiante.

L'ordre dans lequel ces séries d'injections furent administrées eut un effet remarquable sur les résultats, et la première série produisit une amélioration objective très supérieure à celle obtenue avec les séries suivantes, indépendamment de la substance injectée.

Dans l'essai effectué avec des comprimés, il y eut moins de malades améliorés et plus d'empirés avec le *placebo*, que dans l'essai comportant des injections. On discute les causes de cette divergence entre les effets des comprimés factices et ceux des injections factices. En tout, 71% des malades réagirent d'une manière quelconque au *placebo*.

On trouve que les malades qui réagissent au *placebo* ont un indice plus élevé d'introversion et de névrose. Ceux qui réagissent négativement indiquent une tendance à la dominance sociale. On montre que ceux qui réagissent au *placebo* représentent graphiquement un continuum coincidant avec la courbe de distribution normale. On fait une suggestion concernant la manière de conduire les essais cliniques.

Reacciones a substancias farmacológicamente inactivas (*placebos*) en artritis

SUMARIO

Se realizó un estudio terapéutico, utilizando dos esteroides y un *placebo* inyectados, en un grupo de 39 enfermos con artritis reumatoide u osteoartritis implicando la rodilla. En esta publicación se analizan los resultados obtenidos con las inyecciones de *placebo* así como los resultados obtenidos en un otro estudio en el cual el *placebo* fué administrado en forma de comprimidos. Un 25 por ciento mostró una mejoría objetiva con las inyecciones de esteroides y un 18 por ciento con inyecciones de placebo; esta diferencia, siendo el grupo pequeño, no es estadísticamente significativa.

El orden de administración de la series de inyecciones tuvo un marcado efecto en los resultados, produciendo la primera serie una mejoría objetiva muy superior a la obtenida con las series subsecuentes, cualquiera fuera la substancia inyectada.

En la prueba realizada con los comprimidos, menos enfermos acusaron mejoría y más empeoramiento con el *placebo*, que en la prueba con las inyecciones. Se discuten las razones de esta divergencia entre efectos de falsos comprimidos y los de falsas inyecciones. En total, un 71% de los enfermos mostraron reacción de alguna clase al *placebo*.

Se comprobó que los enfermos que responden al *placebo* tienen más indicios de introversion y de neurosis. Aquellos que responden negativamente tienden a ser socialmente dominantes. Representados estadísticamente, las personas que responden al *placebo* forman un contínuo coincidente con una curva de distribución normal. Se presenta una sugerencia referente a la forma de conducir pruebas clínicas.

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PUERPERAL HYPERURICAEMIA

BY

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Elevation of the serum urate levels is well recognized in association with pregnancy toxaemia (Schaffer, Dill, and Cadden, 1943; Chesley and Williams, 1945; Chesley, 1950; Czaczkes, Ullmann, and Sadowsky, 1958). During a study of the incidence of familial hyperuricaemia in toxaemia of pregnancy, a persistent but gradually diminishing hyperuricaemia was noted in a proportion of the patients during the puerperium.

Method

Acceptance to this series as toxaemia of pregnancy was controlled by a rise of blood pressure to 140/90 on at least three occasions, previous readings having been normal, or a rise to 140/90 on one occasion with proteinuria in a previously normal urine. The serum urate was measured on the automatic analyser using Folin's reagent (Folin, 1934). The upper limit of normal in this laboratory is 6 mg./100 ml. If hyperuricaemia was demonstrated during the period of toxaemia, serum urate levels were followed throughout the puerperium.

Results

88 cases were included in the study. The proportion with serum urate and urea abnormality is tabulated below:

No. of Cases	No. with Hyperuricaemia	No. with Raised Blood Urea	No. with Persistent Hyperuricaemia
88	23 (26%)	0	1

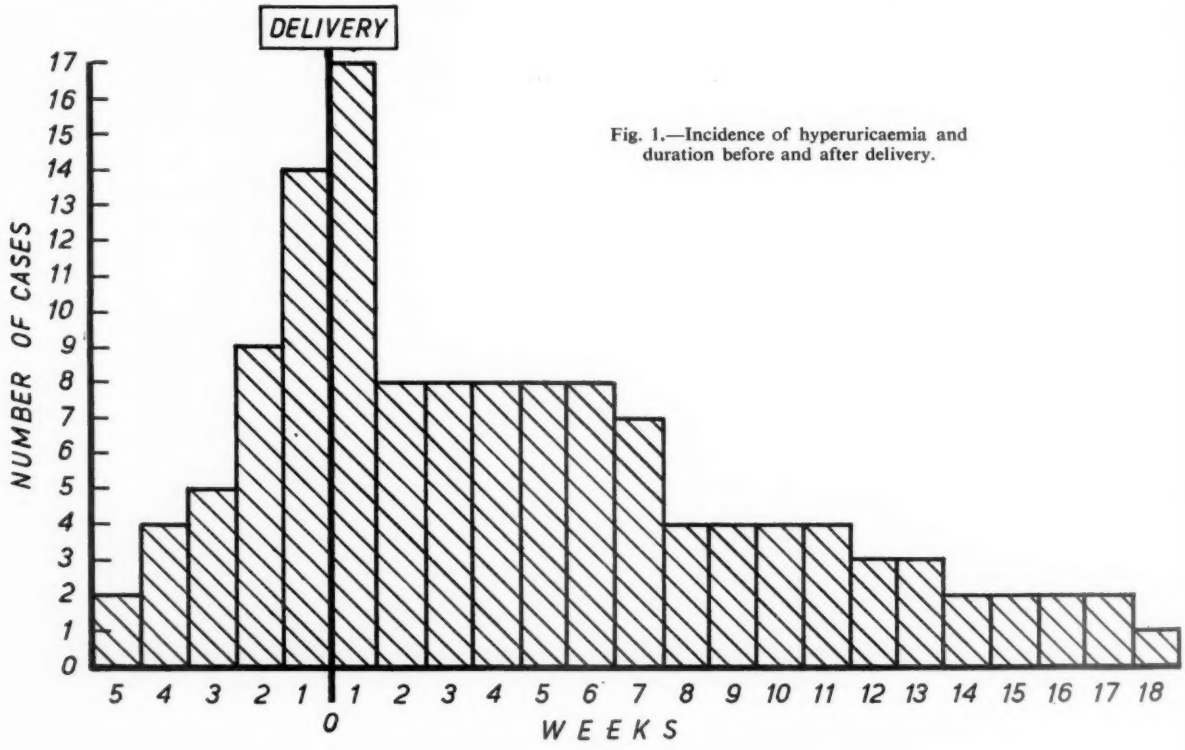

Fig. 1.—Incidence of hyperuricaemia and duration before and after delivery.

One patient had a serum urate level of 6·2 mg./100 ml. after 6 months and was considered to have persistent hyperuricaemia. Urate levels in all the other cases returned to normal.

Fig. 1 illustrates the incidence of hyperuricaemia and its duration in the weeks immediately before and after delivery. It will be seen that seventeen cases were hyperuricaemic during the first week post-partum, eight during the fourth week, four during the eighth week, three during the twelfth week, and two during the sixteenth week.

In Fig. 2 are shown three typical curves depicting toxaemic hyperuricaemia, before and after delivery.

Discussion

Hyperuricaemia initiated by pregnancy toxaemia is not described as continuing for more than a few days into the puerperium. Cadden and Stander (1939) found normal serum urate levels by the fourth post-partum day. Chesley and Williams (1945) observed that the diminished uric acid clearance in eight pre-eclamptics and two eclamptics returned to normal in all cases post-partum, but in two cases it persisted beyond the first week after delivery. Chesley (1950) noted that the uric acid clearance did not rise when the toxaemic syndrome abated with treatment and that it might drop before pre-eclampsia became apparent.

The finding in this series, of hyperuricaemia persisting, although gradually diminishing, in some instances for many weeks after the overt manifestations of toxaemia had subsided, was therefore unexpected.

The fact that probenecid increased urate excretion in pregnancy toxaemia even more than in controls (Czaczkes and others, 1958) suggests that, at least in the cases tested, severe cellular damage was not present. Handler (1960), in showing that the concentration of lactic acid in the blood of toxaemic patients is generally higher than in normal pregnant subjects, suggests that excessive circulating lactate may be partially responsible for the diminished urate clearance—at least during the toxaemic phase. It is difficult, however, to account for post-partum and puerperal hyperuricaemia on this basis, since lactate is rapidly metabolized.

In pre-eclampsia, the glomerular filtration rate and effective renal plasma flow are diminished, sometimes severely so. Pollak and Nettles (1960) have recently described both glomerular and renal tubular lesions in pre-eclampsia. They found a direct correlation between the height of the serum urate and the degree of glomerular disease, and state

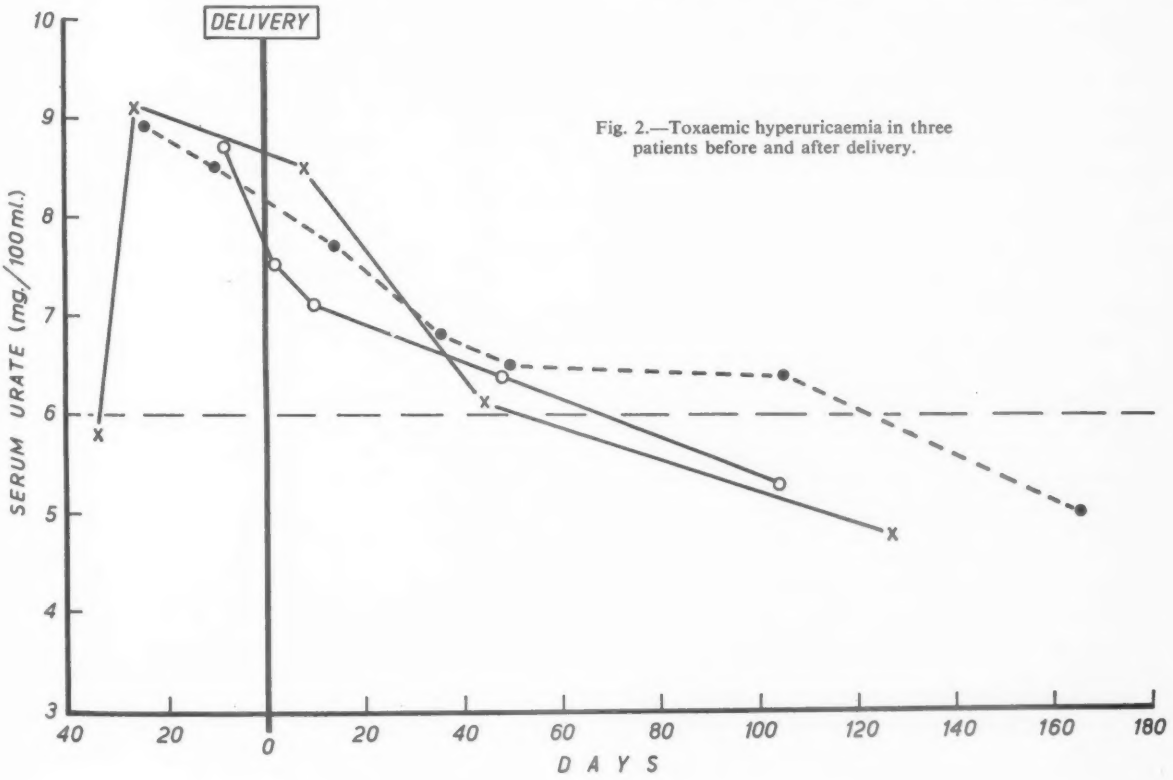

Fig. 2.—Toxaemic hyperuricaemia in three patients before and after delivery.

that " . . . no other clinical or biochemical parameter correlated as well with the glomerular pathology". Serial renal biopsies suggested that permanent glomerular damage occurred when there had been severe glomerular lesions with thickening of the basement membrane. Hyperuricaemia itself appeared to be responsible for progressive destruction of the nephron in the family reported by Duncan and Dixon (1960). The histology of the renal biopsies since obtained from the two youngest members was similar to that of chronic pyelonephritis. In that family hyperuricaemia preceded renal damage. However, it seems more likely that primary renal cellular damage—glomerular, tubular, or both—is at least partially responsible for toxaemic hyperuricaemia. Similarly, puerperal hyperuricaemia may reflect persisting histological changes.

Summary

Serum uric acid levels of 6 mg. per cent. or more were demonstrated in 23 (26 per cent.) out of 88 patients with pre-eclamptic toxaemia of pregnancy, and hyperuricaemia was shown to persist after delivery in seventeen cases for one week, in eight for 4 weeks, in four for 8 weeks, in three for 12 weeks, and in two for 16 weeks. One case remained hyperuricaemic 6 months post-partum. These results, together with the known decrease in glomerular filtration rate and effective renal plasma flow during pre-eclamptic toxaemia, and recent histological studies, suggest that renal cellular damage is responsible for toxaemic hyperuricaemia and that this damage may persist for a variable period into the puerperium.

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Hyperuricémie puerpérale

RÉSUMÉ

Chez 23 (26%) sur 88 femmes en état de toxémie pré-éclamptique on trouva dans le sang un taux d'acide urique de 6 mg./100 cc. ou supérieur et on observa que l'hyperuricémie persista après l'accouchement pendant une semaine dans 17 cas, pendant quatre semaines dans 8 cas, pendant huit semaines dans 4 cas, pendant douze semaines dans 3 cas et pendant seize semaines dans 2 cas. Dans un cas l'hyperuricémia se maintint pendant six mois après l'accouchement. Ces résultats, ainsi que la diminution bien connue de la filtration glomérulaire et de la circulation rénale effective du plasma pendant la toxémie pré-éclamptique, et les études histologiques récentes, font penser que l'hyperuricémie toxémique est due aux lésions cellulaires du rein et que ces lésions peuvent persister pendant une période puerpérale variable.

Hiperuricemia puerperal

SUMARIO

Se encontraron en 23 (26%) entre 88 enfermas con toxemia pre-eclampsica cifras de ácido úrico en sangre de 6 mg. por cien e incluso superiores y se comprobó que la hiperuricemia persistió después del parto una semana en 17 casos, cuatro semanas en 8 casos, doce semanas en 3 y dieciseis semanas en dos casos. En un caso la hiperuricemia perduró durante seis semanas después del parto. Estos resultados, junto con el conocido hecho de la disminución en la filtración glomerular y la circulación efectiva a través del riñon durante la toxemia pre-eclampsica, y recientes estudios histológicos, sugieren que la hiperuricemia toxémica es debida a alteraciones celulares renales y que dichas alteraciones pueden persistir por un período variable en el puerperio.

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ATROPHIC POLYCHONDRITIS
WITH THE REPORT OF A CASE

BY

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During recent years a number of patients have been described in whom degeneration of cartilage in the ears, nose, respiratory tract, and thoracic cage has been associated with polyarthritis and sometimes also with iritis or episcleritis. The first recorded case appears to be that of Jaksch-Wartenhorst (1923) in Prague: a man aged 32 years became ill with multiple arthritis and fever and this was followed by swelling of both external ears, proceeding to shrinkage and deformity, with partial stenosis of the external auditory canals, deafness, and tinnitus; the nasal cartilage collapsed, producing a saddle-nose deformity; the epiglottis became shortened, thick, and nodular; pain and tenderness developed in the costochondral junctions and xiphoid process. Jaksch-Wartenhorst considered that this was a hitherto undescribed degenerative disorder of cartilage and named it polychondropathia.

Von Meyenburg (1936), in Zurich, briefly reported a second case and a full account of the same patient was published by Altherr (1936); neither author was aware of Jaksch-Wartenhorst's earlier paper and they described the condition as chondromalacia. This patient was a boy aged 14 years, who died 10 months after the onset of an illness in which a migrating polyarthritis involving the large joints was accompanied by softening of cartilage in the ears, nose, larynx, trachea, and chest wall. Tracheotomy was required to relieve respiratory obstruction. At autopsy, miliary tuberculosis was found with a primary tuberculous complex in the right lung, but the changes in the joints and cartilages were not tuberculous and appeared to be due to a mixture of degenerative and inflammatory processes. Histological evidence of rheumatic myocarditis was also found.

Gordon, Perlman, and Shechter (1948), in the United States, reported a third case, again without knowledge of the preceding publications. An American Negress aged 34 years developed arthritis of the knees and ankles, associated with fever, swelling of the ears, hoarseness, and tenderness over the sternum and chest wall. This patient also required tracheotomy, and biopsy specimens of cartilage showed a mixture of degenerative and inflammatory changes. A further feature was bilateral iritis and conjunctivitis.

A fourth case, with severe ocular complications leading to blindness, was described by Hilding (1952). In this patient, a woman aged 61 years, progressive polyarthritis was associated with deepening of the voice, deformity of the ears and nose, and softening of the costal cartilages. Harders (1954) recorded a further case, a boy aged 16 years, who also needed tracheotomy and in whom the softening of cartilage involved the nose, ribs, larynx, and trachea, with arthritis and episcleritis. Harders recognized that the disease was similar to that described by Von Meyenburg (1936) and Altherr (1936) and that reported by Gordon, Perlman, and Shechter (1948). Similar cases were published by Rogers and Lansbury (1955), and Bober and Czarniecki (1955), both patients being women, aged 61 and 41 years respectively. Each had ocular manifestations and the patient described by Bober and Czarniecki also required tracheotomy. Harders (1956), in a further publication, mentioned three other cases, diagnosed since his earlier paper, but did not give details.

Another typical case was described by Harwood (1958): a man aged 35 years died of respiratory obstruction. Another patient, a woman aged 63 years, was reported by Klatskin and Katzenstein (1958): this patient also died of respiratory infection secondary to chronic respiratory obstruction. Bean, Drevets, and Chapman (1958) reviewed the syndrome and added yet another case, a woman aged 58 years. Two further cases, a man aged 33 years and a woman aged 29 years, were reported by Pearson, Kline, and Newcomer (1960) in a second full review of the syndrome, in which for the first time Jaksch-Wartenhorst's original case was quoted. At the Sixth International Congress of Internal Medicine, Bean (1960) reported briefly the details of six additional unpublished cases and Gill (1960) reported another case.

It thus appears that less than twenty examples of this remarkable syndrome have been published to date, and so far as we are aware no case has previously been reported from Great Britain. We present in this paper details of a typical case which has been observed by us over the past 5 years, though we only recently became aware of previously reported cases. To anyone familiar with the syndrome diagnosis would present no difficulty, and if its existence becomes more generally known it may well be found to be less rare than now appears.

There is, as yet, no agreement on nomenclature: the terms so far used have included polychondropathia (Jaksch-Wartenhorst, 1923), chondromalacia (Von Meyenburg, 1936; Altherr, 1936); panchondritis (Harders, 1954); polychondritis chronica atrophicans (Bober and Czarniecki, 1955); chronic atrophic polychondritis (Bean, Drevets, and Chapman, 1958); relapsing polychondritis (Pearson, Kline, and Newcomer, 1960). Perhaps atrophic polychondritis describes the essential features of the disorder most accurately and briefly.

Case Report

A married woman aged 64 years was first seen on March 22, 1955, by Mr. W. D. Doey, consultant ear, nose, and throat surgeon to the West Herts Hospital. She complained of difficulty in swallowing and of a sense of constriction in the throat, these symptoms having started one week previously. She was found to have congestion and oedema of the arytenoids and aryepiglottic folds; the vocal cords appeared healthy, but their approximation on phonation seemed to be hampered by the soft tissue swelling; in addition, she had otitis externa with soft swelling of both external auditory meati and some oedema of the skin covering the auricles; the auricular cartilage appeared softer than normal.

She was admitted to the West Herts Hospital on March 24, 1955, and was found to have a persistent irregular fever up to 101° F. The oedema of the arytenoids and aryepiglottic folds rapidly subsided: her nose showed some deflection of the septum to the left and crusting on the left side, but no pus, and *x* rays of the chest and nasal sinuses showed no definite abnormality. There was some discomfort on swallowing and pooling of mucus in the pyriform fossa, but a barium swallow on April 18 showed no abnormality in the oesophagus. Examination of the blood on April 12 showed haemoglobin 10·3 g./100 ml.; packed cell volume 33 per cent.; mean corpuscular haemoglobin concentration 31 per cent; leucocytes 7,000/c.mm. (neutrophils 6,076, eosinophils 28, basopnils 28, lymphocytes 728, monocytes 140); erythrocyte sedimentation rate 59 mm./hr (Wintrobe).

Because of the persistent pyrexia, she was seen by one of us (A.R.K.) on April 13. Apart from the swelling of the ears, the only abnormal findings were those in the respiratory system; movement and air entry were diminished at the left lung base and she was producing mucopurulent sputum. A second *x* ray of the chest (April 14) showed congestive changes at the bases and the sputum yielded a heavy growth of *Staph. aureus*. A catheter specimen of urine was sterile and the blood Wassermann reaction was negative. Blood culture was sterile and serum agglutination titres to *S. typhi*, *S. paratyphi* A, B, and C, *S. typhimurium* and *Brucella abortus* were negative. On April 21 she developed tenderness in both calves and oedema of the legs and was thought to have thrombophlebitis: treatment was started with Dicoumarin and aureomycin (to which the staphylococcus in the sputum was sensitive), but the pyrexia continued and after a week the aureomycin was stopped, though treatment with Dicoumarin was continued for 7 weeks. Further laboratory studies at this time, aimed at elucidating the cause of the persistent pyrexia, served only to confuse the diagnosis. A second catheter specimen of urine (April 25) yielded a heavy growth of *B. coli* sensitive to streptomycin, but a course of streptomycin for 4 days produced no effect on the temperature. Cystoscopy and retrograde pyelography (May 11) showed no abnormality, the ureteric urine specimens being sterile. A further blood count (April 28) showed a fall in haemoglobin to 9 g./100 ml., the leucocyte count being 6,500/c.mm. with a normal differential count, and the erythrocyte sedimentation rate 60 mm./hr. Five further blood cultures were sterile, no L.E. cells were found in films made from the peripheral blood, and the serum proteins were normal (albumin 3·6 g./100 ml., globulin 2·49 g./100 ml.). Serum agglutination reactions, repeated on May 5, showed a rise in titre to *S. typhimurium* "H" from less than 40 to 320; three urine cultures and three stool cultures, however, gave no growth of this organism, and on May 23 serum agglutination titres to *S. typhimurium* were again less than 40.

On May 18 the first symptom of arthritis appeared, the right ankle becoming swollen and painful. A small amount of fluid was aspirated, but culture was sterile. A course of chloramphenicol from May 18 to 25 produced no response and the ankle remained swollen and painful. Later in May, pain developed in the left ankle and in both knees and some of the interphalangeal joints of the fingers became swollen and tender. Progressive depression of the nasal bridge was noticed. The ears became softer with loss of the normal folds and collapse of the meatal orifices. The voice had become hoarse. Fig. 1 (opposite) shows the appearance at this time.

By May 31 the haemoglobin had dropped to 8·5 g./100 ml., the leucocyte count being 7,500/c.mm. with a normal differential count, and the erythrocyte sedimentation rate 63 mm./hr. The urine was reported as containing Bence-Jones protein on June 2, 3, and 4, but the plasma proteins were again normal on June 2. Radiological examination of the skeleton and examination of the sternal marrow (June 6) showed no evidence of myelomatosis. Cultures of the marrow were sterile.

At this stage she was seen by H.R.D., who considered that the condition could be accounted for by rheumatoid

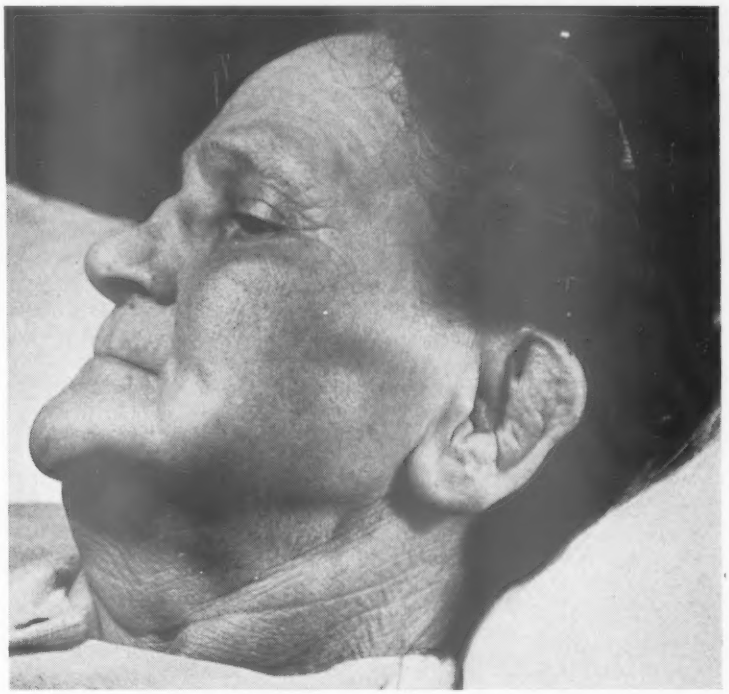

Fig. 1.—General appearance of patient on May 18, 1955.

disease, but had never seen similar involvement of fibrocartilage in this condition. On June 8, therefore, treatment with sodium salicylate in full dosage was begun and the pyrexia, which had hitherto remained persistently between 99° and 101° F., showed an immediate drop to 99° F. or under. The patient's condition began to improve, but by June 27 the haemoglobin had dropped to 7·3 g./100 ml. and the erythrocyte sedimentation rate had risen further to 70 mm./hr. She was therefore given a transfusion of two pints of blood and the haemoglobin had risen to 9·9 g./100 ml. by July 4. A further transfusion of three pints of blood was given on July 9 and on July 12 the haemoglobin was 12·1 g./100 ml. and the erythrocyte sedimentation rate had fallen to 45 mm./hr. On July 22 the differential agglutination test (Rose-Waaler) was positive (16). Treatment with sodium salicylate was continued, but the ankles remained swollen and painful. On August 12 the patient was given 25 mg. ACTH in an intravenous saline drip transfusion over 24 hours; this produced considerable relief for 10 days, but then the knees and ankles again became painful. A second intravenous saline drip containing 25 mg. ACTH was given on August 24, with relief of symptoms over the next month. Pain returned on September 25 and she was given 20 mg. ACTH gel intramuscularly, with only transient relief. On October 1, a third intravenous ACTH drip was given with excellent effect. The pain and swelling in the ankles subsided and she was discharged to her home on October 19, 1955, taking aspirin 10 gr. four times daily. The haemoglobin on September 27 was 11·9 g./100 ml. and the erythrocyte sedimentation rate 50 mm./hr.

On June 6, 1955, she had been seen by Dr. I. Martin-Scott, consultant dermatologist to the West Herts Hospital Group, who commented as follows:

"I have never seen such a picture before. The ear condition seems to be due to swelling of cartilage rather than skin. The areas affected in her pyrexial syndrome are all developed from fibro-cartilage—larynx, ears, and nose."

He suggested biopsy of whole-ear thickness and this was done before discharge. It was reported on by Dr. C. Pike, consultant morbid anatomist to the West Herts Hospital Group, as follows:

"Cartilage of pinna with overlying corium and squamous epithelium bearing hairs and numerous sebaceous glands. At one end of the specimen the cartilage appears normal. At the other extremity it is thickened and broken up into irregular islands, separated by loose fibrous tissue, infiltrated by lymphocytes, plasma cells, and some neutrophils. The cartilage shows altered staining with loss of fuchsinophil fibrils, and thickening of fibres staining with elastica stains" (Fig. 2, overleaf).

Since discharge in 1955, the patient has attended the out-patient clinic regularly. The appearance of her nose and ears has remained unchanged and her voice is still hoarse though less markedly so. The dose of aspirin was gradually reduced from December, 1956, and finally stopped in March, 1957, without any return of joint pain or swelling. The haemoglobin has varied from 12·7 to 14·6 g./100 ml. and the erythrocyte sedimentation rate from 15 to 39 mm./hr. She was last seen by Mr. W. D. Doey in May, 1957, when the larynx appeared to be quite healthy, the vocal cords were healthy and mobile, and the laryngeal cartilage felt quite firm on palpation: no further changes were noticed in the appear-

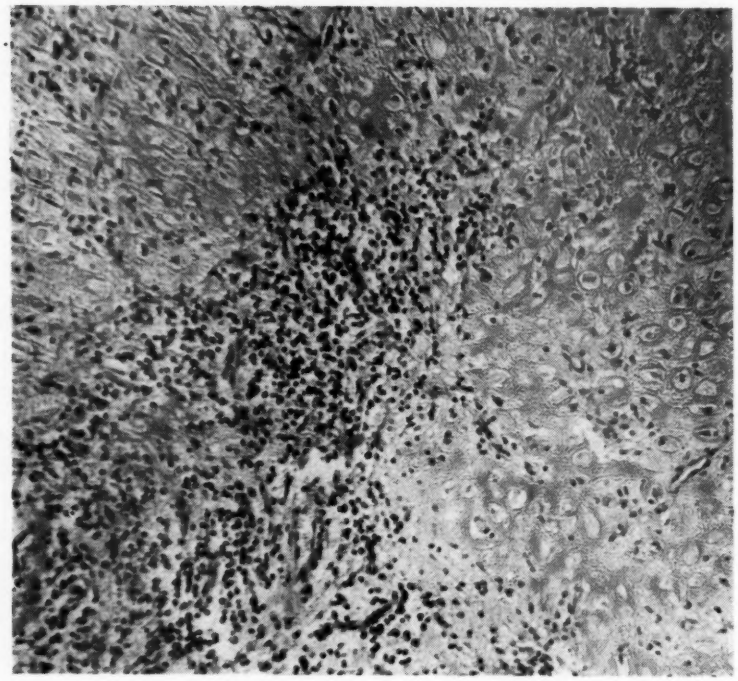

Fig. 2.—Biopsy of the ear, showing cartilage of the pinna broken up by vascular tissue infiltrated by lymphocytes, plasma cells, and some neutrophils. Haematoxylin and Van Gieson.

ance of the auricles, meatal orifices, or nasal septal cartilage.

During the same month, however, she was re-admitted suffering from coal-gas poisoning, having been found lying in front of a gas oven with the tap half on; although she admitted having been depressed for the preceding 2 weeks, she denied any suicidal intention and the episode may have been accidental. She made an uneventful recovery and has shown no further evidence of depression. At her last visit, on September 16, 1960, she was very well.

Discussion

This patient showed the typical combination of cartilaginous degeneration of the ears and nasal septum, leading to deformity, with laryngeal symptoms, respiratory infection, pyrexia, and arthritis. The cartilaginous changes preceded the arthritis, as in the patients described by Von Meyenburg (1936), Harders (1954), Bean, Drevets, and Chapman (1958), and Harwood (1958). But sometimes the order is reversed, as in the cases reported by Jaksch-Wartenhorst (1923), Gordon, Perlman, and Shechter (1948), Hilding (1952), Bober and Czarniecki (1955), and Rogers and Lansbury (1955). No evidence was found of involvement of the costal cartilages or the trachea, and no ocular symptoms occurred. Investigations, as in the previously reported cases, threw little light on the nature of the disease process; anaemia and a raised erythrocyte sedimentation rate during the active phase were of no specific significance and the temporary rise in the *S. typhimurium* agglutination titre was not thought to be of diagnostic value. The presence of Bence-Jones protein in the urine was a puzzling and unexplained finding; it has not been reported in any of the other published cases. There was certainly no other evidence of myelomatosis and the patient's favourable progress over the next 5 years is sufficient to exclude this condition. It is of course known that Bence-Jones protein can occur in other disorders of bone and marrow, such as sarcoma of bone, metastatic bone tumours, senile osteomalacia, fibrocystic disease, lymphatic and myeloid leukaemia, and polycythaemia (Geschickter and Copeland, 1928); it has also been recorded in patients with carcinoma of the stomach and kidney and in a patient with prostatitis and inactive pulmonary tuberculosis (Bayrd and Heck, 1947). Moreover. it is known that anomalous serum protein patterns of the myeloma type may occasionally occur in patients with other diseases, particularly lymphoid reticulosis and macroglobulinaemia (Owen and Rider, 1957). Abnormal serum proteins have also been found in patients with haemolytic anaemia, malignant disease, and numerous other conditions including "rheumatic" disease (Owen and Got, 1960). Unfortunately facilities for electrophoretic examination of the serum proteins were not available to us in 1955, and although the albumin and globulin fractions were quantitatively normal in our

patient's serum, it is possible that electrophoresis might have revealed an abnormal pattern. The most interesting finding was the positive differential agglutination test, which has not been reported in any other case. We do not think that this can be regarded as conclusive evidence that this syndrome is a variant of rheumatoid disease, but it does suggest that there is some inter-relationship. Until we have a much clearer understanding of the real nature of the pathological process in rheumatoid disease and in the so-called collagen disorders, we feel that speculation along these lines is of little value.

The favourable response to ACTH in our patient is in keeping with other reports. Definite improvement with prednisone, with relapse on withdrawal, was observed by Bean, Drevets, and Chapman (1938), and by Pearson, Kline, and Newcomer (1960); some improvement after ACTH was reported by Bober and Czarniecki (1955), and by Klatskin and Katzenstein (1958). Harders (1956) also claimed a favourable response to steroid therapy.

A study of the previously recorded cases shows a remarkable uniformity in the fully-developed syndrome, though the order of involvement of different structures varies: patients may present with aural, laryngeal, respiratory, ocular, or articular symptoms, and are therefore liable to be seen initially in a relatively specialized department rather than by a general physician. The evolution of the complete syndrome may extend over several years. The prognosis is variable: the main danger is respiratory obstruction requiring tracheotomy (Von Meyenburg, 1936; Gordon, Perlman, and Shechter, 1948; Harders, 1954; Bober and Czarniecki, 1955), or causing death (Harwood, 1958; Klatskin and Katzenstein, 1958). If these disasters are avoided, the disease may become quiescent, though the deformities of the ears and nose do not alter. On the present evidence ACTH or steroids appear to be the treatment of choice.

Summary

A case of atrophic polychondritis, under observation for more than 5 years, is described; this is believed to be the first reported in Great Britain. The patient presented with degeneration of cartilage in the ears, nose, and respiratory tract; subsequently she developed polyarthritis, but there were no ocular manifestations, such as have been recorded in some previous cases.

A brief review of the literature is given.

The photomicrograph is reproduced by permission of Dr. C. Pike, to whom our thanks are due.

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Polychondrite atrophique
Avec présentation d'un cas

RÉSUMÉ

On décrit un cas de polychondrite atrophique, observé pendant plus de cinq ans; on croit que c'est le premier cas rapporté en Grande Bretagne. La maladie a commencé avec dégénérescence des cartilages des oreilles, du nez et des voies respiratoires; après cela la malade manifesta une polyarthrite, mais il n'y avait pas de symptômes oculaires du type décrit dans quelques autres cas.

On présente un brève revue de la littérature sur ce sujet.

Policondritis atrófica
Con la presentación de un caso

SUMARIO

Se presenta el que parece ser el primer caso descrito en Gran Bretaña, de policondritis atrófica, sometido a observación durante más de cinco años. La enfermedad comenzó con degeneración de los cartílagos de las orejas, nariz y tracto respiratorio; posteriormente la enferma desarrolló poliartritis, pero no se observaron manifestaciones oculares, del tipo descrito en algunos casos anteriores.

Se realiza una breve revisión de la literatura sobre el tema.

Ann. rheum. Dis. (1961), **20**, 194.

BOOK REVIEW

Controlled Clinical Trials. Conference organized by the C.I.O.M.S. at Vienna, March 23-27, 1959, under the chairmanship of A. Bradford Hill. Pp. 123, 46 figs, bibl. C.I.O.M.S., Paris.

These are the collected and edited papers given at the Conference on Controlled Clinical Trials, called by the Council for International Organizations of Medical Sciences, and held in Vienna in 1959. All the seventeen contributors were from Great Britain, in contrast to the other participants, 64 of whom were invited leaders from European University Medical centres. Fittingly, the chairman was Prof. A. Bradford Hill, since in effect the Conference presented to the rest of Europe what some in Britain have called the "Bradford Hill Revolution", namely, the spread of the statistically controlled clinical trial throughout British Medicine. The story of how this change in medical thought came about has not been told in this book (nor was its object to do so), yet our European colleagues might have understood a little better how their neighbour managed to get ahead in this field if at least one paper at the conference had been devoted to the history of how these trials developed. The trial of streptomycin in pulmonary tuberculosis, for example, although possibly not the earliest, was one of the best known in the early days and owed a great deal of its success not only to the foresight of those who organized it but also to the restricted amount of streptomycin then available. A trial in which the "haves" were compared with the "have nots" became administratively and ethically possible. The introduction of the National Health service in 1948 was perhaps the greatest stimulus, firstly because it overcame many of the financial or transport difficulties (to the patients) of the participating in such trials, and secondly because the authorities of the Health Service needed very much to know the true worth of expensive imported drugs.

The first paper in the book, on "Aims and Ethics", is from Prof. Bradford Hill himself and is a model of clarity. All those who feel instinctively that controlled trials are unethical because the controls may possibly be deprived of some beneficial treatment should read this paper and ask themselves whether they would not agree that in many settings "the carefully controlled clinical trial is far more ethical than the uncontrolled experimentation with unproven products to which unsuspecting patients are so frequently exposed". Indeed, if there were no prior doubt as to the superiority or inferiority of a method of treatment under test, there could be no need for doing a trial at all. As Dr. R. Paterson says elsewhere in the book, when discussing controlled trials in cancer, "The first requirement is that everybody concerned must feel convinced that they could not guess the probable outcome of the study."

The remainder of the book is mainly concerned with technical problems and the presentation of illustrative results. Dr. P. Armitage discusses the problems of the construction of comparable groups, and Dr. D. D. Reid the advantages and disadvantages of using the patient as his own control. Dr. P. Armitage discusses sequential analysis, its application to short-term treatment and its rather more limited application to long-term treatment of the type usually required in the rheumatic diseases. Dr. I. Sutherland discusses the design of records and follow-up procedure, and Prof. J. Knowelden the analysis and presentation of results.

In a paper on rheumatoid arthritis, Prof. J. H. Kellgren discusses the special problems of defining this disease in a reproducible manner. He proposes the following practical definition (for the purpose of clinical trials): "Inflammatory polyarthritis of over 3 months' duration with bilateral involvement of hands or feet associated with a positive sheep-cell agglutination test." He goes on to discuss the various ways in which improvement or deterioration of the disease can be evaluated. Prof. E. G. L. Bywaters discusses the various designs of clinical trial which may be used in rheumatoid arthritis, the problems of what to do about patients who have to be withdrawn before treatment is completed, and other details, and illustrates them with results of the 1955 Empire Rheumatism Council trial of cortisone against aspirin in the treatment of early rheumatoid arthritis. Other papers in the book deal with clinical trials in tuberculosis, cancer, myocardial infarction, and acute respiratory diseases. ALLAN ST. J. DIXON.

HEBERDEN SOCIETY

ANNUAL REPORT, 1960

At the Annual General Meeting held on December 3, 1960, the following decisions regarding membership of the Society were made:

1. Non-medical scientists will be eligible for Full and Associate Membership.
2. Associate Membership will be increased to fifty, vacancies being filled gradually.
3. No alterations will be made to the maximum number of Full Members, but the position will be reviewed in 2 to 3 years.

The following new members were elected:

Ordinary Members: Dr. Rhys Davies, Dr. C. J. M. Clark, Dr. P. S. Davis.

Associate Members: Dr. Charlotte Feldman, Dr.

V. L. Steinberg, Dr. J. T. Scott, Dr. H. Wykeham-Balme, Dr. D. R. L. Newton, Dr. C. Croft, Dr. E. B. D. Hamilton, Dr. Mary Carter, Dr. I. Porter, Dr. W. G. Wenley, Dr. G. Asherson, Dr. J. R. Golding, Dr. R. A. Parkins, Dr. A. Willcox.

Overseas Members: Dr. M. K. Keech, Dr. F. D. Baragar, Dr. J. Webb, Dr. E. Hess.

Continental (European) Members: Dr. J. Forestier, Prof. J. Goslings, Dr. J. J. de Blécourt, Dr. K. A. E. Meijers.

The total Ordinary Membership was thus brought up to 98 and Associate Membership to 29.

The Chairman recorded with regret the deaths of Dr. Philip Ellman and Dr. Stuart Barber, who had been members of the Society for many years.

Activities

At the invitation of Dr. W. S. C. Copeman and Dr. O. Savage, the first clinical meeting of the year was held at the West London Hospital on February 26, 1960 (*Annals*, **19**, 183). Papers were presented by Dr. P. S. Davis (*West London*), Dr. B. G. Parsons-Smith (*West London*), Mr. J. C. F. Hindenach (*West London*), Dr. J. H. Baron (*Middlesex Hospital*), Dr. George Brown for Dr. F. Dudley Hart (*Westminster*), and Dr. O. Savage (*West London*).

A clinical meeting was held at the Royal Infirmary, Manchester, on July 1 and 2, 1960, at the invitation of Prof. J. H. Kellgren (*Annals*, **19**, 380). Papers were presented by Dr. F. Dudley Hart (*Westminster*), Dr. A. J. Popert, Dr. K. A. E. Meijers, Dr. J. Sharp, and Miss F. Bier (*all of the Royal Infirmary, Manchester*), Dr. J. T. Scott (*Hammersmith*), Dr. R. J. Johns (*Leeds*), Dr. R. E. H. Partridge and Dr. J. J. R. Duthie (*Edinburgh*), Miss J. V. Hewitt (*Manchester*), Dr. J. S. Lawrence (*Manchester*), and Dr. J. Ball (*Manchester*).

The Heberden Round was conducted by Dr. W. S. Tegner at the London Hospital on September 16, 1960. Communications were received from Dr. R. M. Mason, Dr. V. L. Steinberg, and Dr. C. R. B. Joyce (*Annals*, **19**, 382).

The Heberden Oration for 1960 was delivered on December 2, 1960, by Dr. J. J. Bunim, M.D., of the Department of Health, Education, and Welfare, National Institutes of Health, Bethesda, Maryland, U.S.A., at the Wellcome Foundation, London, on "A Broadened Spectrum of Sjögren's Syndrome and its Pathogenetic Implications" (*Annals*, **20**, 1).

Dr. Bunim was presented with the Heberden Medal for 1960 by the President.

The Annual Dinner was held on December 2, in the Fellows' Restaurant at the Zoological Gardens, Regent's Park, London. Among the guests present were Lord Nathan, Dr. J. J. Bunim, Dr. F. N. L. Poynter (Wellcome Foundation), Dr. T. F. Fox, and Dr. H. A. Clegg.

The Annual General Meeting was held on December 2 and 3, at the Wellcome Foundation, London. The clinical meeting which followed is reported below (p. 196).

Grant-in-Aid

The Society acknowledges with appreciation the renewal of a grant from the Empire Rheumatism Council.

Library

The Honorary Librarian, Dr. W. S. C. Copeman, reports that during the past year the second edition of the Catalogue of the Society's Library has appeared. This has been circulated not only to members, but, in view of the growing importance and value of the collection, to the principal libraries of Europe and America also.

The Society is very much indebted to the Trustees of the Wellcome Foundation for their generosity, and also to their learned librarian, Dr. F. N. L. Poynter, without whose invaluable help this work would not have been possible.

The collection is gradually becoming a comprehensive and unique one, and the generosity of all members and well-wishers of the Society is invoked for gifts of books or documents bearing upon the subject of rheumatism and arthritis published prior to 1914.

The Ciba Foundation, who had generously housed the library since its formation, required the space to house a recent bequest to themselves. The collection has, therefore, been moved to the Apothecaries' Hall, where the Faculty of the History of Medicine and Pharmacy (to which the Heberden Society is affiliated) have kindly agreed to find room for it.

The following books have been presented (mostly by the Wellcome Trustees) during the year:

AIGNAN, FRANCOIS. Traité de la goutte dans son état naturel. Paris, 1707.

ANHART VON GRATZ, ELIAS. Consilium podagricum. Ingolstadt, 1581.

BOSCH, JOANNES LONAEUS. Kurtzer Bericht von dem Podagra. Ingoldstadt, 1582.

COLBATCH, SIR JOHN. A Treatise of the Gout. London, 1697.

CROONE, WILLIAM. De ratione motus musculorum. Amsterdam, 1667.

EBSTEIN, WILHELM. Die Gicht des Chemikers Jacob Berzelius. Stuttgart, 1904.

FALCONER, WILLIAM. Observations on Dr. Cadogan's Dissertation on the Gout. Bath, 1772.

LE ROY, ALPHONSE L. V. Manuel des goutteux. London (1804?).

OLIVER, WILLIAM. A Practical Essay on the Use and Abuse of Warm Bathing in Gouty Cases. Bath, 1751.

SCOTT, JOHN. Surgical Observations on the Treatment of Chronic Inflammations in Various Structures. London, 1828.

TYLSTON, JOHN. Dissertatio medica inauguralis de rheumatismo. Leyden, 1750.
WYNTER, JOHN. Cyclus metasyncriticus. London, 1725.

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PROGRAMME FOR 1961

Clinical Meeting at the Middlesex Hospital and the Arthur Stanley Institute on February 10.

Clinical Meetings at the Hôpital de la Pitié and the Hopital Cochin, Paris, on May 27, and the Casino d'Enghien-les-Bains on May 28.

The Heberden Round will be held in October.

The Heberden Oration, Annual General Meeting, and Dinner on December 1 and 2.

Titles and short programme notes of original communications which members wish to make to the Society during 1961 should be sent to the Senior Hon. Secretary (Dr. Barbara Ansell, M.R.C.P.) at least one month before the date of the meeting. Abstracts for publication in the *Annals of the Rheumatic Diseases* (approximately 300 words) should be sent in advance or handed to the secretary at the Meeting. Additional meetings will be arranged if necessary.

Annual General Meeting.—The following communications were presented:

DR. MARY CARTER (*Canadian Red Cross Memorial Hospital, Taplow*): **Anatomical Study of Sacro-iliac Joints in Juveniles.**—As part of a study of the incidence and nature of sacro-iliitis in a series of over 200 children at Taplow with juvenile rheumatoid arthritis (Still's disease), an attempt was made to relate the radiological appearance of the sacro-iliac joints to their normal and pathological anatomy.

The sacro-iliac *x* rays of sixty juveniles not suffering from any form of chronic joint disease, of both sexes and various ages, were used to establish normal radiological standards. Four sacro-iliac joints from normal children and two from patients suffering from Still's disease were dissected and the pathological features, both macroscopic and microscopic, were described.

The normal sacro-iliac joints showed broad, smooth sacral cartilage and thinner irregular iliac cartilage with radial "splits" bounding a narrow joint space which was deeper in the anterior part of the joint, the most posterior part being largely filled with fibrous tissue.

The younger of the two rheumatoid patients, who was aged 9 at death, and had showed a doubtfully abnormal right sacro-iliac joint on *x* ray, showed cartilaginous fusion of this right joint without any sign of inflammatory tissue. It was suggested that this might result from the mechanical factor of severe hip disease or previous prolonged immobilization. The other patient, a 20-year-old, whose pelvic *x* ray was normal, showed changes in both sacro-iliac joints with destruction of iliac cartilage and invasion of bony spaces with granulation tissue containing plasma cells and lymphocytes. This change was concentrated in the iliac half of the joint and is in accord with the relative immunity of the thick cartilage and epiphyses in childhood, previously stressed by Prof. Bywaters.

Discussion.—DR. J. BALL (*Manchester*): I should like to take the opportunity of thanking Dr. Carter, not merely because of the intrinsic value and clarity of her paper, but because it seems to underline the remarkable and persistent ignorance of the morbid anatomy of rheumatoid arthritis. We are still not sure what the sacro-iliac joint is really like.

As to Case 2, we had one case of classical rheumatoid arthritis in an adult whose sacro-iliac joint was removed. Radiological signs were absent and the changes were identical to those described by Dr. Carter. There was typical erosive arthropathy affecting only one side of the joint.

As to Case 1, cartilaginous fusion has been described in ankylosing spondylitis. I do not know what this

mean and I do not know how it arises. I have seen this type of change in joints with capsular ossification in rheumatoid arthritis or ankylosing spondylitis and it may be an effect of this type of ankylosis. With the vertical section method used by Dr. Carter, the anterior capsule of the joint, where ossification may predominate, may not be so readily visualized as with horizontal slices.

DR. A. ST.J. DIXON AND DR. E. LIENCE (*Hammersmith Hospital*): **The Sacro-iliac Joint in Adult Rheumatoid Arthritis and Psoriatic Arthropathy.***

DR. B. M. ANSELL AND PROF. E. G. L. BYWATERS (*Canadian Red Cross Memorial Hospital, Taplow*): **Diagnosis of Probable Still's Disease and its Outcome.**—In January, 1959, all patients who had been referred as suffering from Still's disease were reviewed. When strict criteria were applied to those cases in which a clinical picture was compatible with this diagnosis, a total of 43 of the 264 cases followed to date were classed as probably suffering from this disease. During the follow-up period, a definite diagnosis was made in twenty: psoriasis (2), ulcerative colitis (2), further features of classical Still's disease (3), ankylosing spondylitis (2), rheumatic fever (2), osteochondritis (2), systemic lupus erythematosus (1), dermatomyositis (1), Raynaud's disease (1), infectious arthritis (1).

The remaining 23 fell into three main groups: those with systemic manifestations resembling Still's disease in whom rheumatoid arthritis was minimal and joint residua absent; those with transient polyarthritis with minimal residua; those with less than four joints involved who frequently had residua and might represent a mild form of Still's disease.

Discussion.—DR. J. S. LAWRENCE (*Manchester*): I was particularly interested in the cases of transient benign polyarthritis which Dr. Ansell mentioned. Did they occur at any particular time of the year?

DR. ANSELL (*London*): The cases of benign disease were differentiated into two groups and I presume the one you mean is the polyarthritic group. Of the four patients in this group, two occurred in the spring and two in the summer, and three of these show suggestive changes on the neck *x* ray at follow-up.

DR. J. S. LAWRENCE AND DR. J. M. BREMNER (*Manchester*): **Intervertebral Disk Degeneration.**—Disk degeneration as a mark of age is well recognized and in this report the frequency seen on routine spinal films from a population sample in Leigh and Wensleydale has been assessed. Cervical disk degeneration was uncommon below the age of 25 years, but the prevalence rose steadily with age and was more common and severe in males of all age groups. The maximum frequency was at C.5. Dorsal disk degeneration was the one most frequently observed and here was more common, and tended to occur earlier and more severely in females than males, with a maximum prevalence at D.7 in females and D.8 in males. The lumbar spine was not *x*-rayed below the age of 35 and by then disk degeneration was seen in 35 per cent. of males with a maximum affection at L.3. As in the cervical region it was more common and more severe in males. In the cervical spine there was a significant relationship between cervical disk degeneration and neck, shoulder, and brachial pain, the association being greater in females and more striking under the age of 45. Lumbar disk degeneration was found to correlate well with incapacity from back, hip, and sciatic pain in males. Differences were noticed between urban and rural populations, in that the disease was more evenly distributed between the sexes in the rural area and the changes in the lumbar region were earlier in onset.

Discussion.—DR. A. ST.J. DIXON (*Hammersmith*): I was very interested in this magnificent piece of work. I should like to ask one question. From observations one makes in the autopsy room, it is clear that most older people have this type of disk degeneration you have been talking about; but in some old people we fail to see it. Have you noticed any familial reason why such people *escape* this degeneration?

DR. LAWRENCE (*Manchester*): No, I think a combination of factors is involved, and constitution is unimportant. People with cervical disk degeneration do not necessarily have lumbar disk degeneration. There seems to be some correlation if you take a mixed occupation group, but groups of cases all following one occupation show no correlation of the two sites.

DR. J. FORESTIER (*Aix-les-Bains*): Dr. Lawrence described with beautiful pictures a number of changes in disk degeneration. Were these samples taken from one case followed up over a number of years, or were they taken from several cases? I should also like to know if Dr. Lawrence can give us any information about the influence of trauma in these cases. It is a very important medico-legal question affecting workers in industry which has arisen in every country. When pain appears in a man's spine, and the disk appears altered radiologically, how far is the trauma responsible and how far is normal disk degeneration responsible?

DR. LAWRENCE: The *x* rays were chosen from the population samples of different people, and are those we are using as standard films for grading.

With regard to association with trauma. When one compares people with a history of injury to the back with those who have not, one finds that there is often more pain in those who have had an injury, but that the *x*-ray changes are the same. The injury brings out the symptoms but does not affect the disease.

DR. H. F. WEST (*Sheffield*): Do I detect a note of despair in Manchester? Surely, if physiological is *normal* functioning, *pathological* is the converse, and no degeneration can be described as physiological. We must find the cause.

DR. R. HARRIS (*Buxton*): The difference between radiological changes and symptoms is important. The highest disability rate was found in young people who had shown marked disk degeneration. People do not

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stay away from work because of marked changes, but presumably because of an acute disk prolapse.

DR. LAWRENCE: I do not altogether agree. I think pain can occur without disk prolapse, but this is difficult to prove. Most people with nerve trunk pain do not show any physical signs of disk prolapse, and the pain is more likely to be referred. Admittedly the condition is so asymptomatic that some other factor must be involved. There is already a mechanical disadvantage and slight trauma is enough to produce manifest symptoms.

PROF. E. G. L. BYWATERS, DR. M. CURWEN, DR. E. DRESNER, AND DR. A. ST.J. DIXON (*Hammersmith Hospital*): **10-year Follow-up Study of Rheumatoid Arthritis.**—250 cases of rheumatoid arthritis first seen between 1939 and 1948, 125 of them within one year of the onset of disease, have been followed to date. The general pattern was similar to that of other published series of rheumatoid arthritis, there being a predominance of females and a mean age at onset of approximately 45 years. At the 10-year follow-up, 78 of the total of 250 were dead, 76 were in the top two functional grades, and 96 in the lower three functional grades. Further follow-up information has revealed that 131 are now dead.

The causes of death are largely the ordinary ones and show a close resemblance to a series published some years ago by the Boston group. It appeared that patients who were going to die suffered a reduction in their functional capacity before death, but this was not necessarily caused by the rheumatoid arthritis, but might be due (for example) to a coronary thrombosis. It could not be said that death was due merely to age, as in the late series death tended to occur at a younger age than in the early series, and the overall mortality was greater than the expected.

Taking in more detail the 125 early cases, and considering their 5-year follow-up, certain points seemed to emerge. Younger patients did better than older patients, males did better than females, and those with asymmetrical involvement and fewer joints involved did better than those with more joints involved. A negative D.A.T. at follow-up was also a good prognostic feature and females with a negative D.A.T. did better than females with a positive D.A.T. The diagnosis of psoriasis also seemed to improve prognosis. The mean functional status at the 5-year follow-up was Grade 4 and at the 10-year follow-up it was Grade 3·92. Eight patients had died by the 5-year follow-up and 29 by the 10-year follow-up. It was concluded that variability in the course of rheumatoid arthritis was associated with many different factors, the relationships of which were obscure. Death, when it occurred, was very rarely due to specific complications of the disease, but tended to occur from the usual causes at an earlier age.

Discussion.—DR. J. BALL (*Manchester*): I have a strong impression that aged people who die and who have suffered with rheumatoid arthritis for many years show atherosclerosis less than one would expect. It is difficult to quantitate this, but I should like to know what Prof. Bywaters thinks.

PROF. BYWATERS (*Taplow*): I cannot give Dr. Ball any definite information. Much more work has to be done on this and it would require a prospective study, but my impression is the same as his.

DR. F. DUDLEY HART (*Westminster*): How many of the 131 who died were under the age of 65 years?

PROF. BYWATERS: I should have to have notice of that question.

DR. L. C. HILL (*Bath*): I should like to ask Prof. Bywaters whether he had the impression, only an impression as far as I am concerned, that the mode of onset of the rheumatoid arthritis affected the prognosis? I have had a feeling in watching patients that those who start with polyarthritis, marked constitutional symptoms, sweating, and rapid development of anaemia do surprisingly well, while in those who catch the doctor napping, starting with a single joint and few systemic features, the rheumatoid arthritis develops relentlessly.

PROF. BYWATERS: I have not been able to make an analysis of this particular point. It was one of Dr. J. J. R. Duthie's conclusions from his series, and we did try observing those who started with a high erythrocyte sedimentation rate, but it is a difficult point to analyse unless you go back to the beginning and classify those with a slow start and those with a vigorous start.

DR. M. THOMPSON (*Newcastle-upon-Tyne*): This point was investigated in eighty patients with acute onset who were documented by Duthie and others. This was a prospective study, and it has been adequately confirmed. I should like to ask Prof. Bywaters if he was impressed, even in this antibiotic era, by the amount of sepsis, and whether the forms of sepsis might be accounted for by inactivity or as a true predilection of the disease.

PROF. BYWATERS: I think many factors enter into this. I am not sure how the cases of infection in this series compared with cases in other hospitals. This matter of choosing controls or making comparisons is extremely difficult.

DR. A. G. S. HILL (*Stoke Mandeville*): Returning to this question of acute onset. Looking into 25 sero-negative patients, all seen within a year of onset, we checked these points by picking twice the number of sero-positives, matched for duration. When we compared these two groups the incidence of acute onset was about the same in both, but the sero-negative cases were more often admitted to hospital because they were more severely ill.

The haemoglobin fell lower and the erythrocyte sedimentation rate and serum proteins rose higher. After this a high erythrocyte sedimentation rate persisted for 3 to 6 months, and the patients then got better and progressed towards recovery. It is these cases that Dr. L. C. Hill has in mind.

PROF. BYWATERS: I think, however, that there is a tendency to improve in the first year, and particularly in the first 5 years, whatever groupings you have. It is the question of whether the rate of improvement is bigger in one group or another.

DR. A. G. S. HILL: Sero-positives do well but sero-negatives do rather better.

DR. R. M. MASON (*London*): Did Prof. Bywaters find an association of peripheral neuropathy to be a bad prognostic sign? We have been impressed by patients developing a peripheral neuropathy and quite a high percentage died within a couple of years. Or does he regard this as a "red herring"?

PROF. BYWATERS: It may well be. It has not entered into this 10-year survey, as peripheral neuropathy develops after a long period, but in comparison with other cases such patients go downhill fast.

PROF. J. H. KELLGREN (*Manchester*): May I ask the duration of disease in those admitted in their terminal illness. You seem to have excluded a number of these people who died very recently.

PROF. BYWATERS: We excluded thirty of 280, of which seventeen died in hospital. We did not bother to analyse them any further, but I think most of them had had the disease a long time.

DR. F. DUDLEY HART, DR. J. R. GOLDING, DR. J. R. HOYLE, DR. R. G. MANLEY, DR. D. A. P. STRICKLAND, AND DR. M. O'SULLIVAN (*Westminster Hospital*): **Investigation of Peripheral Nerve Lesions in Rheumatoid Arthritis.**—It is well recognized that peripheral neuropathy is a complication of rheumatoid arthritis and may be part of a generalized disorder, or due to local compression of a nerve by a swollen and disorganized joint. It is suggested that it is usually possible to differentiate these two types of neuropathy by an investigation of ischaemic and post-ischaemic paraesthesiae of the affected limb, but this technique has its limitations. To assess autonomic nerve function, sweating experiments were carried out by warming the patient, usually by immersion in a bath, when it was found that there was considerable delay in autonomic function. An ingenious method of assessing vibration sense showed that it tended to diminish with age and was not as good in subjects with rheumatoid arthritis, but without neuropathy, as in control subjects of similar age. Interdermal histamine confirmed the presence of peripheral nerve degeneration, but was of no value in early cases.

Discussion.—DR. L. C. HILL (*Bath*): As one gets older there are disadvantages, in that it is more difficult to take in these complicated charts and chemical formulae; one of the advantages is that one begins to see the natural history of the disease a little better. I have been impressed over the years by the changing history of diabetes, both in complications, severity, and expectation of life, and I have also been interested in the changing pattern of rheumatoid arthritis, particularly in the direction of neuropathy, and of destructive changes in the weight-bearing joints. I think they are manifestations of the same thing. Destructive changes occur in weight-bearing joints in diabetes, and I believe they are manifestations of diabetic neuritis. I am willing to believe that there are neurological complications in rheumatoid arthritis, which have greatly increased through the use of long-term steroids. I am sure that steroids alter the natural history of a disease such as rheumatoid arthritis and increase the tempo in the direction of systemization.

DR. R. M. MASON (*London*): Were the patients who showed this diminished vibration sense any different from the rest?

DR. GOLDING: No, it was a completely unselected series. We did not assess the duration of this symptom and most of the cases were on aspirin only.

DR. G. R. FEARNLEY (*Gloucester*): I wonder whether one might consider employing this elegant technique with vibration sense to osteo-arthritis as well as rheumatoid arthritis. This idea occurred to me about 10 years ago, but I was too lazy to design such an apparatus. It might give a measure of co-ordination. One wonders whether the osteo-arthritis occurs in those patients with not such good co-ordination.

PROF. J. H. KELLGREN (*Manchester*): Does this technique measure vibration sense in bone or vibration in the skin?

DR. GOLDING: This vibration sense seems to come from the skin and the deep tissues. I do not think it comes from the bone, because we found that the finger tips and toe tips were more sensitive than the ulnar styloid.

PROF. J. H. KELLGREN: Could changes in structure alter the test, *e.g.* dry skin, sweating, atrophy, etc. Since many rheumatoid patients have atrophy of the skin, were you measuring changes in the skin texture?

The sweating test is a magnificent method of getting objective evidence, particularly in patients with only sensory changes; could not the patients unable to get into the bath be tested by "cooking" them in an electric blanket?

DR. GOLDING: We used the electric blanket in one or two cases. We made no measurements regarding skin except to exclude patients whose skin was particularly calloused or thick.

PROF. E. G. L. BYWATERS (*Taplow*): Did you measure vibration sense, for example, up the finger? Did you measure sense at the bottom only or compare this with its threshold at the tip? It would be interesting to do this in view of the changes we are to discuss later.

DR. GOLDING: We did not do this, partly because it takes time and later on the fatigue phenomenon is involved. One has to use only a few points.

DR. K. N. LLOYD (*Cardiff*): You seem to have excluded the question of bone taking part in the sensation; have you used the machine over the calf and fleshy areas?

DR. GOLDING: Yes, we have done this and the vibration can still be felt there.

DR. F. CLIFFORD ROSE (*London*): I am interested in this early loss of vibration sense that Dr. Golding has found in his cases of diabetic neuropathy. Autonomic changes are said to be among the earlier manifestations. It is possible that the different types of loss may be related to the size of nerve fibre.

Has the bath any advantages over the heat cradle in testing for sweat functions, as it does seem more difficult to use?

DR. A. J. POPERT (*West London Hospital*): **Pregnancy in Patients receiving Steroid Therapy for Rheumatic Diseases.**—This was an attempt to study the course of the disease and to discover whether steroid therapy had any effect on the mother or the foetus. The series comprised seven patients with rheumatoid arthritis, five with systemic lupus erythematosus, and five with ankylosing spondylitis. It covered 27 pregnancies, during which treatment with corticosteroid and corticotropin was administered in thirteen cases. It was not possible to relate foetal deaths to the treatment that the mother had received during pregnancy. The oral administration of corticosteroid had no influence on the fertility of the mother, no ill-effects on the child, and no effect on the course of the disease, but corticotropin was probably

in a different category because of the variety of side-effects produced by total adrenal stimulation.

Discussion.—DR. F. DUDLEY HART (*Westminster*): When I inquired about this a few years ago, Dr. Popert seemed to be the only source of information. It is obviously important to know whether there is any threat to the pregnancy in mothers who have been taking steroids.

DR. B. M. ANSELL (*Taplow*): One of our patients, who had been maintained on steroids, had a baby with a cleft palate. This young woman illustrates another problem that we have encountered amongst juveniles who have been on steroids. She had had periods of amenorrhoea with a negative Hogben test, and because we did not know exactly when she became pregnant we did not reduce the dosage of steroids. We have had three examples of this problem, and also a small group of married women between 20 and 30 years of age, of whom three have had a definite miscarriage on at least one occasion when they were hoping to have a family.

DR. POPERT: Miscarriages are said to occur in 10 per cent. of pregnant women, but I think there are more studies to be done before we can say anything definite.

Cleft palate is one of the important bogies. Dr. Fraser found that massive dosages of cortisone would produce cleft palate in the mouse, but others have failed to reproduce his observations. Only one human case has been reported in which cleft palate might possibly have been due to cortisone; Harris reported that 300 mg. a day had been given during the period when it was estimated that the palatal process would normally be developed. It cannot be denied that cortisone might have been the cause in this case, and I should be interested to have more details of Dr. Ansell's case.

PROF. E. G. L. BYWATERS (*Taplow*): This is a very important subject of practical interest. This series is too small to be able to say exactly what happens, but it should be a function of this Society to assist studies of this nature by airing the subject so that those of us who wish to do so may contribute to it. We have all had cases of this nature and I am sure we and others would be able to contribute to the series.

DR. POPERT: I should be delighted to receive details of such cases from any and every source.

DR. J. H. GLYN (*London*): I am very interested in the toxaemia case which occurred 6 weeks after steroids had been withdrawn. In 1951 a paper came from Dr. A. Moore and his collaborators in Ireland, who regarded steroids as an acceptable treatment for toxaemia.

One other question: have you had any experience of patients who become worse in pregnancy and are subsequently improved by steroids. I have had one or two intriguing cases of this kind.

DR. POPERT: We had at least three who grew worse and who subsequently did well on steroids.

On the subject of toxaemia. It has been suggested that some abnormality in the corticosteroid metabolism may be the reason. As you know, Moore thought such patients were well treated on corticosteroids, but later results show that corticosteroids have no place in the treatment of toxaemia.

REFERENCE

Moore, A., Jessop, W. J. E., O'Donovan, D. K., Barry, A. P., Quinn, B., and Drury, M. I. (1951). *Brit. med. J.*, 1, 841.

DR. J. T. SCOTT, DR. D. O. HOURIHANE, DR. F. H. DOYLE, DR. R. E. STEINER, DR. J. W. LAW, DR. A. ST.J. DIXON, AND PROF. E. G. L. BYWATERS (*London*): **Digital Arteritis in Rheumatoid Disease.***

Clinical Meeting.—At a meeting held on February 10, 1961, at the Middlesex Hospital, the following papers were read:

DR. J. D. NABARRO AND DR. R. E. COTTON (*Middlesex*): **A Case of Ankylosing Spondylitis.**—A woman's symptoms of ankylosing spondylitis began at the age of 22 in 1928, followed one year later by typical ulcerative colitis. Both the colitis and the ankylosing spondylitis appeared to progress over the next 12 years and she become bedridden because of hip involvement in 1940. In 1947 successful bilateral hip arthroplasties were performed. About this time she first developed iritis and in 1952 a basal diastolic murmur was heard. Subsequently, in her final illness, which was associated with inflammation of the remaining colon, she developed a mycotic aneurysm of the subclavian artery, myocardial infarction, and probable bacterial endocarditis, and died shortly after an operation for the removal of the remaining part of the colon. The *post mortem* findings consisted of complete bony fusion of the whole spine, colitis in what remained of the gastro-intestinal tract, and in the cardiovascular system rheumatic heart disease, aortitis with atheroma, coronary occlusion, and an aneurysm at the junction of the right subclavian with the common carotid artery.

MISS M. D. SNELLING (*Middlesex*): **Treatment of Ankylosing Spondylitis by Deep *X* ray.**—Radiotherapy should be used early in the disease when improvement in pain allowed the patient to receive vigorous physiotherapy, but once complete ankylosis has occurred it is of no value. Of the various possible complications, skin necrosis no longer occurs with present-day dosages, and although there was no absolutely safe level of dosage, leukaemia is unlikely.

DR. J. W. STEWART (*Middlesex*): **Effect on the Bone Marrow of Treatment with Deep *X*-ray Therapy for Ankylosing Spondylitis.**—In the course of deep *x*-ray therapy for ankylosing spondylitis, the bone marrow in the bones of the spine and part of the pelvis receives a heavy dose of irradiation. The bone marrow from 130 patients undergoing deep *x*-ray therapy at the Meyerstein Institute of Radiotherapy has been examined before, during, and at intervals after treatment.

The standard treatment consists of 2,000 rads to the whole spine and sacro-iliac joints in the course of eight to ten treatments over a period of 3 to 4 weeks. The immediate result is the cessation of haemopoiesis in the irradiated marrow. Recovery usually started between 3 and 6 months after the cessation of treatment, but is often incomplete and the bone marrow may remain hypoplastic for many years.

Some patients have received two courses of irradiation at this dosage. In approximately half the cases, no

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recovery was observed even after several years, and the remainder have shown poor recovery, the marrow being markedly hypoplastic.

Several patients have been treated with 1,200 rads. In these the immediate result of treatment is the cessation of haemopoiesis, but recovery of the marrow starts after 3 to 6 weeks and, though proceeding slowly, is more rapid and in most cases more complete than in patients treated with larger amounts of irradiation.

Discussion.—DR. R. DOLL (*London*): I was much interested in these observations on bone marrow, which fit in with the observations of Jacobs and Court-Brown in Edinburgh on the effect on chromosomes of small doses of irradiation. Over a period of 2 weeks these workers have been taking daily samples of blood after a variety of doses ranging from a skin dose of 250 r to the lumbar, dorsal, and cervical vertebrae down to a skin dose of 75 r; the latter dose approximates to 30 r to the marrow which is still bigger than the dose which Stewart told us produces aplasia. With all dosage levels it has been possible to detect chromosome abnormality for the whole fortnight. At the 75 r level, abnormalities are probably present, but at 125 r they are definite; in view of the progressive decrease with reduction in dose, it would seem that the dose produces the abnormalities. Abnormalities of all kinds are found; they include ring chromosomes and concentric chromosomes, but the commonest change is production of fragments. It is not possible to say how long these changes may continue to be seen or how long they can be detected, because the patient needs treatment and a fortnight is the longest interval the clinician will allow before it is repeated. They have not seen a culture return to normal after treatment and this fits in extremely well with the beautiful pictures shown by Dr. Stewart.

DR. H. F. WEST (*Sheffield*): After the war I was much interested in this subject and I ran a radiotherapy clinic for 3 years, using large doses, but the radiation did not appear to affect the course of the ankylosing spondylitis. 9 years ago we were told that the association between radiotherapy and leukaemia in our cases could not be ignored. I have not used radiotherapy for 10 years and have not felt we needed it, having got just as good results without.

DR. R. M. MASON (*London*): I should like to second this. I wonder whether Dr. Stewart, if he got ankylosing spondylitis, would have a course of radiotherapy himself?

DR. STEWART: I don't know a better treatment. I have been impressed with the results of *x*-ray therapy in these patients. These patients are crippled, and many of them have left it late before coming for advice. X-ray treatment, especially if followed with physiotherapy to keep the muscles active, enables them to move without pain, quickly and without fear of falling. I have not had the advantage of seeing Dr. West's improved treatment, but in the cases we have treated with 1,200 r, although it is too early to be sure, the number of cases of leukaemia is likely to be very small, less than a half or a quarter of one per cent., and I would not let that 0·25 per cent. deter me from having radiotherapy.

DR. G. D. KERSLEY (*Bath*): There are these two opposite views; some would use a machine gun to keep the radiotherapist away and some are in love with her. The answer probably lies somewhere between the two. The older members will have heard these extremes posed in various phases of medicine. There are certain cases, where the question of irradiation of the ovaries does not come into the picture and where the patient is in pain which could be relieved by radiotherapy, and it is a question of weighing the problem in individual cases.

MR. P. H. NEWMAN (*Middlesex*): **Osteotomy of the Spine.**—Thirteen patients with severe kyphosis associated with ankylosing spondylitis were treated by osteotomy of the lumbar spine, with a very careful regime of pre- and post-operative care. One of the most troublesome post-operative features was meralgia paraesthetica.

There had been no deaths as a result of surgery, but one patient had developed empyema which necessitated treatment in the sitting position, causing loss of correction. Four patients were shown. Three had a good posture and in one there was some recurrence of the kyphosis. There was a disappointing tendency for the initial correction to regress slowly as the years passed.

Discussion.—DR. J. H. GLYN (*London*): Does Mr. Newman think that this operation will have much application in the future in view of the availability of steroids; furthermore, we have altered our attitude to the treatment of ankylosing spondylitis so that patients are given active physiotherapy instead of being immobilized. I have not seen a recently crippled case for many years, and I wonder if such cases are not a residue of past methods.

MR. NEWMAN: I have done very few such operations in the last few years; there were many after the war, but they have now tailed off.

MR. W. D. COLTART (*London*): I have not seen many such cases for the last few years. Does Mr. Newman think that this loss of correction is gradual, or does it happen fairly quickly after a certain space of time. And what is the reason for the meralgia paraesthetica?

MR. NEWMAN: Most of the loss of correction occurs in the first 2 years and then tails off gradually. With regard to the meralgia paraesthetica, we broke the spine at the level of L2/3 and tended to have a hyper-extension of L2, and I presume that it was merely mechanical. In middle-age, meralgia paraesthetica may develop simply by extending the spine. We relieved it by cutting the nerve.

DR. FRANK SCADDING (*London*): I should like to dispel a myth that such patients are particularly subject to respiratory disease, for we have followed up very many cases at the Brompton Hospital, and respiratory disease was no more frequent than in the rest of the population. An exception was a woman who, in addition to her severe arthritis, had a fibroma, which was removed by Mr. Holmes Sellors; she developed a thrombosis after operation and a hospital-acquired staphylococcus. She had empyema, and this was tapped (through a hole in her jacket) and then drained surgically.

DR. G. D. KERSLEY (*Bath*): I was interested in Dr. Scadding's remarks, for I must say that one does not see many pulmonary complications in ankylosing spondylitis as compared with rheumatoid arthritis, etc. The pulmonary complications of spondylitis were, however, so drummed into us in the past that one is still apt to teach one's students to look out for them. It is therefore very useful to have this fallacy pointed out.

DR. F. M. ANDREWS (*London*): **Treatment with G.27 202.**—The immediate effects of this drug were reported to the Society in 1959 and this is a report of a follow-up. Of the 33 patients who were being maintained on this treatment, 31 had definite rheumatoid arthritis and two ankylosing spondylitis. The dosage was usually 400 mg. daily, but two received 500 mg. daily and two 300 mg. daily, salicylates being taken by the patients as required. The duration of the follow-up varied from 14 to 23 months, and sixteen of the patients followed to date required no other analgesics. The reduction in morning stiffness noted by these patients seemed to be significant. Eight had stopped treatment for various reasons, two because of severe dyspepsia. This side-effect was seen in four others in a milder form and other side-effects noted were lymphoedema in two, not previously reported, ankle oedema in four, mouth ulcers in four, anorexia in one, and pruritus in one. No bone marrow depression was seen.

DR. E. J. M. CAMPBELL (*London*): **Respiratory Function in Rheumatic Disorders.**—In rheumatoid arthritis and some other disorders of connective tissue, a diffuse interstitial pulmonary fibrosis develops which causes the so-called alveolar-capillary block syndrome. In this condition there is increased stiffness of the lungs which reduces the vital capacity and requires increased effort in breathing, but does not seriously impair the breathing capacity or cause ventilatory failure. Gas exchange between pulmonary blood and alveolar air is disturbed, increasing the wasted (dead-space) ventilation and interfering with the transfer of oxygen much more than with that of CO_2. Anoxia, particularly on exercise, rather than CO_2 retention is the pattern of respiratory failure seen in this syndrome and oedema (cor pulmonale) is rare.

In ankylosing spondylitis the resting lung volume is increased, but the vital capacity is reduced. There is little reduction in breathing capacity and no disturbance of gas exchange in the lungs. Respiratory failure (anoxia or CO_2 retention) rarely occurs.

Gross distortion of the thoracic cage in kyphoscoliosis may reduce vital capacity and breathing capacity to such an extent that ventilatory failure (CO_2 retention) and oedema (cor pulmonale) often occur. Gas exchange in the lungs is little affected so anoxia develops only when the underventilation is severe.

Discussion.—DR. A. ST. J. DIXON (*Hammersmith*): Have you any information on variation of lung function with time of day as regards vital capacity and stiffness? We are familiar with morning stiffness in the joints, and I wonder whether the internal organs show the same change.

DR. CAMPBELL: Measurement of compliance is a crude technique, and I doubt if it could detect such changes. I know of no such observations.

DR. W. G. WENLEY (*London Hospital*): We have regularly measured respiratory, inspiratory, and expiratory flow rates in ankylosing spondylitis. The inspiratory slope is flatter, which is different from that seen in emphysema. We thought it was probably due to costovertebral involvement.

DR. C. J. M. CLARK (*Bournemouth*): In patients with rheumatoid arthritis, is there any relationship between radiological changes in the chest and disturbed respiratory function?

DR. CAMPBELL: I am unaware of any correlation between pulmonary function and radiology in any disease!

DR. T. M. CHALMERS AND DR. J. R. HEARNSHAW (*Middlesex*): **A Case of Scleroderma treated with Relaxin.**—A man aged 59 with scleroderma had presented 2 years previously with Raynaud's phenomenon followed by tightening of the skin on hands and face. Although some improvement followed the use of Priscol and prednisolone, the patient developed atrophic changes of the finger tips, and a brachial arteriogram confirmed gross narrowing of the vessels to the fingers. He was given a 3-week course of Relaxin (Releasin: Wm. R. Warner and Co.) in March, 1960, and there was evidence of both subjective and objective improvement, which was maintained for some months. A further course again produced improvement, but the patient is now beginning to deteriorate again. In order to be effective prior treatment with stilboestrol is necessary. Relaxin is expensive and may be difficult to obtain.

Discussion.—DR. J. H. GLYN (*London*): I understand from my hospital dispensary that Relaxin costs 50*s.* per injection, and that in any event supplies have been temporarily suspended. Is it therefore likely that it will ever be practicable long-term treatment? Since steroids appear to have some effect on this disease, would it be possible to maintain patients with this cheaper form of treatment once Relaxin has proved effective or would the two drugs antagonize each other?

DR. HEARNSHAW: It keeps very well if refrigerated, certainly up to 3 or 4 months. Initial treatment with Relaxin followed by steroids seems to be a reasonable approach. In this particular case, the patient had a relapse on prednisolone and again developed atrophic changes in a finger previously affected by gangrene. The drug is rather too expensive for long-term treatment, and intermittent treatment is therefore necessary.

DR. H. F. WEST (*Sheffield*): This seems to be an enormous dose. Is most of it destroyed before it gets in, and can this destruction be prevented?

DR. HEARNSHAW: We have no information on this, but I discussed the dosage with Warner and Co. Patients in America have been maintained on 10-15 mg. a day, being less than half the amount required to bring initial improvement. The average dose at which noticeable benefit occurs is 40 mg.

In conclusion, MR. R. T. TURNER WARWICK described a soft-tissue biopsy instrument with which clean-cut cylinders of tissue of any consistency short of bone could be obtained, and also a modified Akerman vertebral biopsy instrument.

Ann. Rheum. Dis. (1961), **20**, 203.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Protracted Relapsing Rheumatic Carditis. Its Association with Chronic Tonsillitis and Its Prevention and Treatment. [In Russian.] MJASOEDOV, E. S. (1960). *Ter. Arh.*, **32**, 39. 12 refs.

The author reports the results in 78 patients suffering from rheumatic fever who were followed up after tonsillectomy for 1 to 2 years. Protracted relapsing rheumatic carditis was diagnosed in 37 (47 per cent.), while the disease was inactive in 41 (53 per cent.); a proportion of the latter group showed evidence of valvular lesions and circulatory failure of Grades I and II. After tonsillectomy 58 per cent. of the patients improved, 29 per cent. failed to do so, and 13 per cent. deteriorated.

Tonsillectomy appears therefore as only one of the measures to be employed in the treatment of acute rheumatism and the author suggests the following course of treatment, which should last 1½ to 2 months:

(1) Two 10-day courses of penicillin or tetracycline separated by a 5 days' interval.
(2) A search for and elimination of septic foci.
(3) Administration of ascorbic acid (0·1 to 0·2 g.) vitamins B_1 and B_2 (0·001 g. of each), and 0·1 g. of vitamin P, all these doses being given three times a day for 3 or 4 weeks.
(4) Either "pyramidon", 0·24 g. six to nine times a day for 3 or 4 weeks (with frequent blood examinations), or 0·5 g. of aspirin six to eight times a day for 2 to 3 weeks, gradually reducing the dose, or 0·15 g. phenylbutazone three times a day to a total dose of 18 g.
(5) 20 to 40 units ACTH (corticotrophin) daily up to 1,000 units, or cortisone, 0·025 g. four times daily for 4 weeks.
(6) In the absence of circulatory failure, small blood transfusions of 75 to 125 ml. every 5 days.
(7) Administration of bromides and caffeine to maintain the tonus of the nervous system.

If there is circulatory failure treatment should include cardiac supportive therapy, such as tincture of strophanthus, Bekhterev's mixture, or digitalis, and a low-carbohydrate diet, limited salt and fluid intake, and ample calcium. Finally physiotherapy and remedial exercises are given as indicated.

Uniform improvement was achieved in 252 patients thus treated, of whom 87 per cent. had valvular disease. The erythrocyte sedimentation rate returned to normal in 55 per cent. and was reduced to 10 to 20 mm. in one hour in a further 28 per cent. Since the introduction of the above method of treatment the mean mortality has fallen from 14 per cent. (the rate in 1953-54) to 3·1 per cent., and the incidence of subacute bacterial endocarditis has been reduced practically to *nil*. *S. W. Waydenfeld.*

Cerebrovascular Accidents in Rheumatic Fever. [In Russian.] MIHEEV, V. V. (1960). *Sovetsk. Med.*, **24**, 31.

Rheumatic fever may occasionally be complicated by various types of cerebrovascular accident, such as thrombosis, non-thrombotic softening, subarachnoid haemorrhage, cerebral haemorrhage, and less often cerebral embolism. Since any of the cerebral arteries may be affected the clinical picture is highly variable. In the absence of evidence of hypertensive disease or of syphilis an erroneous diagnosis may easily be made. The author states that cerebrovascular complications occur more often and are more severe in rheumatic fever than in other collagen diseases, probably owing to its protracted course and associated cardiac lesions. The condition must be differentiated from infections of the central nervous system, aneurysm, or influenzal haemorrhagic encephalitis. *S. W. Waydenfeld.*

Sydenham's Chorea without Evidence of Rheumatic Fever: Report of its Association with the Schönlein-Henoch Syndrome, and with Systemic Lupus Erythematosus, and Review of the Literature. PARADISE, J. L. (1960). *New Engl. J. Med.*, **263**, 625. 45 refs.

Biological Study of Rheumatic Fever in Childhood with reference to 100 cases treated with Phenylbutazone. (Une étude biologique de la maladie de Bouillaud chez l'enfant. A propos de 100 cas traités par la phénylbutazone.) LAPLANE, R., SALBREUX, R., POLONOVSKI, CL., and SARFATI, J. (1961). *Ann. Pédiat.*, **37**, 200. 11 figs, 52 refs.

Coordinated Approach to the Prevention of Rheumatic Fever. SHAFFER, J. D., and THOMPSON, W. B. (1961). *Sth. med. J.* (*Bgham, Ala.*), **54**, 65. 1 fig., 10 refs.

Frequency of Rheumatic Heart Disease in Northern Israel: Autopsy Findings. WINTER, S. T., GRIFFEL, B., and REISNER, S. H. (1960). *Acta med. orient.* (*Tel-Aviv*), **19**, 279. 12 refs.

Use of Triamcinolone in the Treatment of Children with Rheumatic Fever and Chorea. (A propos de l'utilisation de la fluoro-delta-hydrocortisone en thérapeutique infantile. (Rhumatisme articulaire aigu et chorée rhumatismale.)) POTOCKI, M. B. (1961). *J. Med. Lyon.*, p. 195.

Renal Damage in Rheumatic Fever in Children. (Choroba reumatyczna a nerki.) GERKOWICZ, T., and LEWICKA-URBÁNSKA, B. (1960). *Pol. Tyg. lek.*, **15**, 1770. 8 refs.

Treatment of Acute Inflammatory Rheumatism (Rheumatic Fever and Reiter's Syndrome) with Diacetylpyrocatecholcarboxylic Acid and its Injectable Derivative. (Le traitement des rhumatismes inflammatoires aigus (maladie de Bouillaud et syndrome de Fiessinger-Leroy-Reiter) par l'acide diacétyl-pyrocatecholcarboxylique et son dérivé injectable.) MASBERNARD, A. (1960). *Thérapie*, **15**, 1224. 16 refs.

Immunologic Studies of Heart Tissue. III. Occurrence of Bound Gamma Globulin in Auricular Appendages from Rheumatic Hearts. Relationship to Certain Histopathologic Features of Rheumatic Heart Disease. KAPLAN, M. H., and DALLENBACH, F. D. (1961). *J. exp. Med.*, **113**, 1. 46 refs, 4 plates.

IV. Serologic Reactions with Human Heart Tissue as revealed by Immunofluorescent Methods: Isoimmune, Wassermann, and Autoimmune Reactions. KAPLAN, M. H., MEYESERIAN, M., and KUSHNER, I. (1961). *J. exp. Med.*, **113** 17. 30 refs, 4 plates.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Erythropoiesis in Rheumatoid Arthritis: The Effect of Spleen Extract and Amino Acid Solution on Bone Marrow Cultures. [In English.] HAMMERSTEIN, G., JONSSON, E., LINDGREN, G., NERI, A., NETTELBLADT, E., PLUM, C. M., and SANDELL, B.-M. (1960). *Acta rheum. scand.*, **6**, 81. 7 refs.

A study of the relationship between spontaneous erythropoietic activity and disease is reported from Södersjukhuset, Stockholm. Samples of bone-marrow tissue from 54 patients, of whom 23 had rheumatoid arthritis and the remainder various other diseases, were cultured. The cellular layer was obtained by centrifugation and diluted to a count of 30,000 to 50,000 cells per c.mm. This material was divided into six separate samples: two with added serum from the same patients, two with 1 per cent. of a splenic extract stated to have an erythropoietic effect (Goldberg and others, *Acta physiol. scand.*, 1950, **22**, Suppl. 77), and another two with added amino-acid solution similar in composition to the splenic extract. After 4 to 5 hours of culture a cell count was made to determine an increase or otherwise in the number of cells.

No difference in activity was found between the bone-marrow cultures from patients with rheumatoid arthritis and those from patients with other disorders. When, however, splenic extract was added, a significant enhancement of activity occurred in the cultures from cases of rheumatoid arthritis, but not in those from the controls. With the amino-acid solution there was a similar increase in erythropoiesis in cultures from the arthritic group, but results in the other cases were inconclusive.

[Unfortunately, no normal controls appear to have been included in this series.] *G. Loewi.*

Large Cysts in Lower Leg originating in the Knee occurring in Patients with Rheumatoid Arthritis. HARVEY, J. P., JR., and CORCOS, J. (1960). *Arthr. and Rheum.*, **3**, 218. 8 figs, 19 refs.

Popliteal cysts communicating with the knee-joint are common in patients with rheumatoid arthritis. Such cysts, which were extensive, reaching well down the calf and lying either between muscles or between muscle and tibia, were seen in four patients admitted to the Hospital for Special Surgery, New York, all of whom had had rheumatoid arthritis for some years and had been treated with steroids. Considerable hydrarthrosis was present originally; this was followed later by tender swelling of the calf suggesting thrombophlebitis. The cystic nature of the calf swellings was not always apparent clinically, but arthrograms clearly showed their extent and their communication with the knee-joint. In three cases the cysts were excised, with recurrence in two and involvement of the other leg later in one. The cyst walls were fibrous without specific cellular lining; in places a palisade-like arrangement of fibroblasts and collections of lymphocytes and plasma cells were seen.

It was uncertain whether the cysts developed by herniation of the synovial cavity of the knee between semimembranosus and gastrocnemius muscles, or by the breaking down of a dividing wall between the joint cavity and a preformed cyst. It is suggested that steroid therapy may have played a part in causing weakness and stretching of the fibrous wall of the synovial cavity and of the cyst. *J. A. Cosh.*

Long-term Use of Phenylbutazone in Rheumatoid Arthritis. MASON, R. M., and STEINBERG, V. L. (1960). *Brit. med. J.*, **2**, 828. 2 figs, 9 refs.

The results of long-term administration of phenylbutazone in 315 patients with rheumatoid arthritis and the findings at the end of 4 years are described in this paper from the London Hospital. In the majority of patients the dosage ranged from 100 to 400 mg. daily, but of twelve who had up to 1,200 mg. daily for short

periods, two developed intolerance to the drug. In some cases treatment brought about a remission and in others it was ineffective. At the end of 3 months the drug was discontinued in 37 per cent. of the patients, after 2 years in 80 per cent., and after 3 years in 88 per cent. Intolerance was the commonest reason for discontinuing the drug, particularly in the early stages of treatment. Symptoms of intolerance were observed in 15·9 per cent. of the patients during the first 3 months and in only 27·7 per cent. at the end of 3 years; after 3 years no further cases of intolerance were encountered. Gastro-intestinal symptoms and rash were the commonest toxic manifestations, but stomatitis, oedema and blood dyscrasias were also observed. At the end of 3 months, 198 of the patients were taking phenylbutazone, seven of them being in remission; at the end of 2 years, the figures were 62 and two respectively, and at the end of 3 years, 45 and 0 respectively. The number of patients in whom the drug was ineffective and therefore withdrawn was ninety in the first 3 years and in three in the fourth year; only 38 patients continued to take the drug after 4 years. The incidence of remission was highest between the 6th and 24th months of treatment, but some remissions were observed up to 3 years. The authors consider that the longer the patient takes phenylbutazone the less likely is the development of intolerance. They regard this as an indication for continuing treatment for a long time in the hope of achieving a remission and avoiding steroid therapy with its very toxic effects. *William Hughes.*

Acute Infectious Arthritis in the Aged and Chronically Ill. WILLKENS, R. F., HEALEY, L. A., and DECKER, J. L. (1960). *Arch. intern. Med.*, **106**, 354. 1 fig., 21 refs.

This is an account of nineteen cases of acute septic arthritis in aged or chronically ill patients seen during a 5-year period at the King County and Seattle Veterans Administration Hospital, Washington. In fifteen cases the diagnosis was based on the culture of organisms from the synovial fluid, in one case organisms were identified in a smear of the joint fluid, and in three cases the presentation and clinical course were characteristic. The patients' ages ranged from 45 to 77 years. In sixteen cases the arthritis was monarticular and in three polyarticular. The knee-joint was most commonly involved, then the shoulder, interphalangeal joints, ankle, and elbow, in that order. In nine cases the infecting organism was *Staphylococcus aureus*, which in some cases was resistant to the usual antibiotics, and in at least three of these there was reason to believe the infection had been acquired in hospital. The next commonest organism was the pneumococcus. In twelve cases the infection appeared to be blood-borne from infection elsewhere (pneumonia, empyema, superficial infection, osteomyelitis). In six cases the infection entered the joint by penetrating trauma, which in three cases was intra-articular therapy. Four patients had chronic rheumatoid arthritis and eight were chronic alcoholics.

In eleven cases conservative therapy with antibiotics was used and the results appeared to be as good as in cases treated by open drainage in addition to antibiotics. If adequate antibiotic therapy was instituted promptly the results were good. The diagnosis was difficult in some cases owing to failure to realize that an increase in joint symptoms was not due to an exacerbation of pre-existing arthritis or disease. The importance of paracentesis of the joint whenever there is doubt is stressed. The "leukocrits" of joint fluid from successive paracenteses were valuable for following progress. Vancomycin proved helpful in some of the cases due to resistant staphylococci. *C. Bruce Perry.*

Non-infectious Arthritis in Small Bones and Joints. SCALF, R. F., and LING, JI-TOONG (1961). *Arch. intern. Med.*, **107**, 23. 5 figs, 16 refs.

Modern Management of Rheumatoid Arthritis. GOLDING, D. N., and THOMPSON, M. (1961). *J. Irish med. Ass.*, **68**, 1. 7 figs, 12 refs.

Gold Therapy in 100 Cases of Rheumatoid Arthritis. (La chrysothérapie de la polyarthrite chronique évolutive (A propos de 100 observations).) VIGNON, G., BOUVIER, M., PERRIN-FAYOLLE, M., and MAZADE, J. (1960). *Rev. lyon. Méd.*, **9**, 1155. 40 refs.

Oral Administration of Gold in Cases of Rheumatoid Arthritis. (Aplicacion peroral de oro en casos de poliartritis progresiva.) LENOCH, F., VOJTISEK, O., and KRALIK, V. (1960). *Arch. argent. Reum.*, **23**, 81. 19 refs.

Lymphography in Rheumatoid Arthritis. (Polyarthritis chronica progressiva v lymfografickém obraze.) KRIEGEL, F., MÁLEK, P., BELÁN, A., and KOLC, J. (1961). *Čas. Lék. čes.*, **100**, 65. 15 figs, 6 refs.

Rheumatoid Arthritis and "Deltabutazolidin". (Artritis reumatoide y delta-butazolidina.) DE LA PRADA ARROYO, M. (1960). *Rev. esp. Reum.*, 7, 584. 15 refs.

Results of Treatment with Antimalarials in Rheumatoid Arthritis. (Resultados obtidos pelo uso de antimaláricos na artrite rheumatóide.) GAMARSKI, J. (1960). *Rev. bras. Med.*, **17**, 599. 11 refs.

Rheumatoid Arthritis and Polyneuritis. (Polyarthrite rhumatoide et multinévrite.) COSTE, F., DELBARRE, F., BASSET, F., and RONDOT, P. (1961). *Sem. Hóp. Paris*, **37**, 399. 12 figs, 27 refs.

(Osteo-Arthritis)

Aseptic Barotraumatic Osteonecrosis of the Hip. (Study of the Early Radiological Lesions. Relationship with Early Osteo-Arthritis.) (L'ostéonécrose aseptique barotraumatique de la hanche. Étude des lésions radiologiques précoces. Rapports avec la coxarthrose au début.) JAFFRES, R., and MERER, P. (1960). *Rev. Rhum.*, **27**, 454. 10 figs.

Pathogenesis of Aseptic Barotraumatic Osteonecrosis and Osteo-Arthritis of the Hip. (Considerations pathogéniques sur l'ostéonécrose aseptique barotraumatique de la hanche et sur la coxarthrose.) JAFFRES, R., and MERER, P. (1960). *Rev. Rhum.*, **27**, 467. 1 fig., 24 refs.

Classification and Treatment of Arthritis of the Hip. (Classification et traitement des coxarthroses.) DE SÈZE, S., and LEQUESNE, M. (1960). *Ann. Méd. phys.*, **3**, 243.

Effect of Weight-Bearing Exercises on Radioactive Sodium Clearance from Normal and Osteo-Arthritic Knee Joints. WISHAM, L. H., DAVISON, S., and GORDON, L. (1960). *Arch. phys. Med.*, **41**, 587. 2 refs.

Quality and Duration of Remissions of Osteo-Arthritis occurring after *X*-ray Therapy. HARVEY, N. D. M. (1960). *J. Coll. Radiol. Aust.*, **4**, 101. 4 figs, 4 refs.

(Ankylosing Spondylitis)

Rheumatoid Spondylitis: A Follow-up Study. LEFKOVITS, A. M., and THOMAS, J. R. (1961). *Ann. intern. Med.*, **54**, 12. 4 refs.

Uveitis and Ankylosing Spondylitis. (Zapalenie jagodówki w zesztywniającym zapaleniu stawów kręgosłupa.) MONDELSKI, S., and MROCZKOWSKA, B. (1961). *Pol. Tyg. lek.*, **16**, 170. 19 refs.

Pain caused by Cervical Spondylitis. BRADSHAW, P. (1961). *Rheumatism*, **17**, 2. 15 refs.

Ankylosing Spondylitis and the Radiological Integrity of the Sacro-iliac Joints. (Spondilite anchilosante ed integrità radiologica delle sincrondrosi sacro-iliache.) BARBASO, E. (1961). *Rheumatismo*, **12**, 366. 4 figs, 43 refs.

(Miscellaneous)

Hippocratic Fingers and Hypertrophic Osteoarthropathy: a Study of 350 Cases. COURY, C. (1960). *Brit. J. Dis. Chest*, **54**, 202. 8 figs, 16 refs.

This account of "Hippocratic fingers" (H.F.) and hypertrophic osteo-arthropathy (H.O.A.) is based on 350 cases studied at the Hôpital Hôtel-Dieu, Paris. Over 80 per cent. of the patients were males. The changes seen in H.F. are regarded as the first stage in the development of H.O.A., which in its complete form also shows hypertrophy of the distal portions of the upper and lower limbs, pains in the joints, bilateral proliferative periostitis, and peripheral neuro-vascular disorders (cyanosis, excessive sweating, and paraesthesiae). These two conditions and other related syndromes have been grouped under the general term "dysacromelias".

In this series infective respiratory disease was present in more than 50 per cent. of patients with H.F., but H.O.A. occurred more commonly in association with lung cancer, 80 per cent. of the patients with H.O.A. being diagnosed as suffering from cancer of the lung and 10 per cent. as suffering from a malignant tumour of the pleura. In the study of this condition laboratory investigations were not found to be of particular value, although urinary steroid excretion was often low in those patients who had developed gynaecomastia, which occurred much more often in those with H.O.A. than in those with H.F.

The author concludes that simple clubbing of the distal phalanx is likely to be due to a chronic infection or fibrotic disease of the chest and that the complete changes of H.O.A. are more often brought about by a tumour of the lung. Gynaecomastia combined with H.O.A. is highly suggestive of intrathoracic malignant disease. He accepts the view that the local abnormalities are due to functional changes in the precapillary circulation of the extremities and that the visceral changes are due to vascular shunts in the pulmonary circulation or the physiological equivalent thereof. The pathogenesis of the connexion between the thoracic starting-point and the distal receiving-point is unknown, although it is postulated that there seems to be a predisposing factor in certain individuals. *A. Gordon Beckett.*

Non-group-A Streptococci in Rheumatic Patients and Their Possible Significance in Postinfectious Rheumatism. [In English.] JONSSON, J. (1960). *Acta rheum. scand.*, **6**, 3. 49 refs.

At the Department of Rheumatology, Karolinska Sjukhuset, Stockholm, specimens from the throat of 700 patients, who were examined during a period of 2 years (1957-59), were cultured. The antistreptolysin-O titre (A.S.O.) was estimated in the serum of every patient. Of the 43 strains recovered, 39 could be grouped serologically according to Lancefield's system. Almost half the strains were isolated during an epidemic of Asian influenza (November, 1957, to March, 1958). The proportion of Group-G strains was unduly high (about 50 per cent., while that of Group-A strains was low (about 25 per cent.). A rise in A.S.O. may be caused by infection with C and G strains, but not by B strains, the pathogenicity of which appears to be very low. Immunological response is known to increase in rapidity and strength from birth to 10 to 20 years, but elevation of the A.S.O. titre does not run parallel with the clinical course of rheumatic fever, a rise often persisting after subsidence of clinical symptoms.

After listing the criteria by which post-infectious rheumatism is diagnosed, the author points out that the proportion of Group-G strains was so high (about 65 per cent.) and that of Group-A strains so low (about 18 per cent.) that it is unlikely that the latter can be mainly responsible for this condition; in rheumatic fever, on the other hand, Group-A strains are undoubtedly incriminated. *D. Preiskel.*

Experience with Punch Biopsy of Synovium in the Study of Joint Disease. RODNAN, G. P., YUNIS, E. J., and TORTEN, R. S. (1960). *Ann. intern. Med.*, **53**, 319. 5 figs, 21 refs.

The authors of this paper from the University of Pittsburgh School of Medicine, Pennsylvania, report their findings on examination of 142 specimens from 136 patients of synovial tissue obtained from knee-joints affected by rheumatic disease by means of the instrument for punch biopsy described by Polley and Bickel (*Ann. rheum. Dis.*, 1951, **10**, 277; *Abstr. Wld Med.*, 1952, **11**, 70). Specimens were taken from three different sites from the suprapatellar bursa distended either with synovial fluid or by the introduction of 40 to 60 ml. 0·85 per cent. sodium chloride solution. The histological appearances were compared with those of 75 specimens taken at necropsy from open knee-joints clinically free from disease. Correlation of "sclerotic atrophy" with advancing age was obtained. The punch biopsy specimens were grouped according to histological appearances into:

(1) no disease;

(2) non-specific synovitis;

(3) questionable rheumatoid arthritis (focal accumulations of lymphocytes, small numbers of plasma cells, minimal oedema, fibrosis, and vascular proliferation, and occasional deposits of fibrin or fibrinoid);

(4) rheumatoid arthritis (more pronounced inflammatory focal reaction, prominent number of plasma cells, and, in some cases, pronounced vascular proliferation); and

(5) other "specific" synovitis (gout, scleroderma, and neuropathic joint disease).

Of 26 patients with rheumatoid disease and active involvement of the knee, the changes in 24 were considered to be "at least in the category of questionable rheumatoid arthritis" and in seventeen "were sufficient to place the patients in the category of rheumatoid arthritis". None of the patients with clinically inactive disease gave evidence of active synovitis. Relative acuteness of the inflammatory process was related to the presence of large amounts of fibrin or fibrinoid and numbers of neutrophil polymorphonuclear leucocytes. The authors state that these changes are not specific for rheumatoid arthritis, "being noted as well in cases of systemic lupus erythematosus and psoriatic arthritis. Marked hyaline thickening, atrophy and vascular sclerosis of the synovium were observed in a number of patients with progressive systemic sclerosis (diffuse scleroderma), and are changes which appear to be pathognomonic of this disease. While urate deposits were detected in the synovium of a number of patients with long-standing gout, the lack of these in many patients with well documented disease (including several with acute gouty geniculitis at the time of biopsy) suggests that tophaceous matter *per se* plays little part in the development of acute gouty arthritis. Punch biopsy of the synovium has proved to be a simple, safe and practical procedure which may supply information of considerable value in the study and diagnosis of joint disease".

There was only one complication of the procedure; a man with myeloma and a bleeding tendency had pain and swelling of the knee which subsided following aspiration of bloody synovial fluid from the distended joint. *Harry Coke.*

Reiter's Syndrome and Keratosis Blennorrhagica. SHATIN, H., CANIZARES, O., and LADANY, E. (1960). *A.M.A. Arch. Derm.*, **81**, 551. 2 figs, 23 refs.

The authors discuss the relationship between these diseases on the basis of published papers. Keratosis blennorrhagica may follow either Reiter's syndrome or a gonococcal infection, and they suggest the name be abandoned in favour of the term "Reiter's syndrome" with modifying terms, *e.g.* Reiter's syndrome with keratoderma. *W. E. S. Bain.*

Studies of Arthritis and Other Lesions induced in Rats by Injection of Mycobacterial Adjuvant. III. Lesions of the Eye. WAKSMAN, B. H., and BULLINGTON, S. J. (1960). *A.M.A. Arch. Ophthal.*, **64**, 751. 6 figs, 35 refs.

The hind foot-pads of rats were injected with a single dose of heat-killed tubercle bacilli suspended in mineral oil. About 65 per cent. of animals developed severe arthritis and other lesions of the mucous membranes and skin, while 15 per cent. also developed iridocyclitis. Most animals had an acute non-granulomatous uveitis, but a few showed features of granulomatous uveitis with iris nodules and mutton-fat keratic precipitates. These manifestations were thought to be a delayed hypersensitivity reaction as no organisms could be cultured from the ocular tissues. The possible relationships between this symptom complex in the rat and Reiter's disease, Behçet's syndrome, and ankylosing spondylitis are discussed. *R. F. Fisher.*

Physical Medicine in Rehabilitation after Arthritis in Children. KNAPP, M. E. (1960). *J. Amer. med. Ass.*, **174**, 1951. 3 figs.

Clinical, Radiological, and Electrocardiographic Characteristics of Changes in the Cardiovascular System in Patients with Rheumatoid Arthritis. (Caratteristiche cliniche, radiologiche ed elettrocardiografiche delle alterazioni dell'apparato cardiocircolatorio nei malati di artrite reumatoide.) EINAUDI, G., and VIARA, M. (1960). *Reumatismo*, **12**, 299. 78 refs.

Hypertension in Cases of the Schönlein-Henoch Syndrome. (Nadciśnienie w Przebiegu Zespołu Schönleina-Henocha.) ASKANAS, A. (1960). *Pediat. pol.*, **35**, 1441.

Dupuytren's Contracture and its Surgical Treatment. HEYSE, W. E. (1960). *J. Amer. med. Ass.*, **174**, 1945. 18 refs.

Gout

Uric Acid Dust as an Aetiological Factor in Occupational Gout. [In Russian.] LUK'JANOV, V. S., NIKITSKIJ, I. N., and PUŠKINA, N. N. (1960). *Gig. Truda prof. Zabolev.*, **4**, 6. 2 figs.

Gout has been described as an occupational disease among workers engaged in the collection, drying, and preparation of dung at poultry farms, an industry which is now carried out on a large scale, the dung being used for the manufacture of uric acid. In spite of the wearing of protective clothing, considerable opportunities exist for the absorption of uric acid through the lungs, gastro-intestinal tract, and possibly also the skin.

After doing this work for 2 or 3 years the workers developed pains in the joints, especially of the hands and feet, accompanied by crepitus, while firm tender tophi in the fingers and toes were observed in some cases. Signs of increased muscular excitation were present and Chvostek's sign was positive. Toothache and dental caries were frequently complained of. The urine contained a high concentration of urates and the blood uric acid level was raised in 43 out of 52 persons examined, the actual values being correlated with the duration of exposure to this type of work. On change of occupation manifestations of the disease disappeared. *Basil Haigh.*

Treatment of Acute Gout with Steroids. (Tratamineto del Ataque de Gota con Esteroides.) MORENO, A. RUIZ (1960). *Arch. argent. Reum.*, **23**, 96.

Problem of Uricolysis: Results of Clinical Experimental Studies and a Possible New Method for the Treatment of Certain Aspects of Gout. (El problema de la uricolisis: Estudios clínicoexperimentales, resultados de los mismos y posible nuevo método para el tratamiento de ciertos aspectos de la gota.) BARCELÓ, P., PUIG MUSET, P., and SANS SOLÁ, L. (1960). *Rev. esp. Reum.*, **7**, 537. 14 figs, 57 refs.

Hepatocatalase: New Treatment for Gout. (L'epatocatalasi. Nuovo trattamento della gotta.) BARCELÓ, P., PUIG MUSET, P., SANS SOLÁ, L. (1960). *Rheumatismo*, **12**, 181. 13 figs, 57 refs.

Metabolism and Pharmacology of Sulphur in relation to Gout. (Rapporti della gotta con il metabolismo e la farmacologia dello zolfo.) CAMPANACCI, D., and GIRO, C. (1961). *Rif. med.*, **74**, 13. 5 figs.

Pararheumatic (Collagen) Diseases

Current Therapy of Systemic Lupus Erythematosus. A Comparative Evaluation of Corticosteroids and Their Side-Effects with Emphasis on Fifty Patients treated with Dexamethasone. DUBOIS, E. L. (1960). *J. Amer. med. Ass.*, **173**, 1633. 18 refs.

In the first part of this paper from the University of Southern California School of Medicine, Los Angeles, the author presents an excellent summary of his personal clinical experience of 400 cases of systemic lupus erythematosus (S.L.E.) and of the principles he has applied in therapy. [But the majority of rheumatologists and others unfamiliar with the author's previous writings will hesitate to accept his opening sentence, which states: "Systemic lupus erythematosus . . . is a malignant variant of rheumatoid arthritis."] The second half of the paper records the results of the treatment with dexamethazone (9α-fluoro-16α-methylprednisolone) of fifty patients suffering from S.L.E. and compares the side-effects observed in this series with those in previous series treated respectively with methylprednisolone (40 cases), triamcinolone (29), and prednisone and prednisolone (37). [The method of sequential comparison adopted by the author is inacceptable to many authorities as a valid basis for comparison. Further, the period of treatment varied from one to 15 months and the steroid therapy was supplementary to other forms of treatment; thus 24 patients received salicylates to the point of mild toxicity and seventeen were taking antimalarial drugs. Again, 29 patients received dexamethasone as their initial steroid therapy, but 21 were transferred to this drug from treatment with other steroids. Also reference is made to one of the author's series in which 38·7 per cent. of the patients exhibited spontaneous improvement before steroid therapy was even begun. Lastly, no detailed analysis of the severity or of the duration of the disease before steroid treatment was started in these fifty cases is given.]

The dosage of dexamethasone varied from 1 to 6 mg. daily, usually in two divided doses, but in two critically ill patients a dosage of 24 mg. daily was employed for 2 to 3 weeks. The pattern of clinical improvement with dexamethasone paralleled that in previous series in which other steroids were used. However, a higher percentage of dexamethasone-treated patients (especially those initially treated with the drug) exhibited Cushingoid features, more insomnia, and a greater degree of pitting oedema—28 per cent. compared with a mean of 3·6 per cent. for the other steroid preparations. In a special study of the incidence of peptic ulcer, fourteen patients underwent base-line radiographic studies before the start of dexamethasone therapy and these, together with thirteen others, were examined radiographically at varying intervals thereafter. [It is difficult from the information provided to understand the rationale for selecting the patients or deciding the time intervals between the radiographs.] This study revealed six new peptic ulcers after periods of therapy ranging from 2 to 18 months, all of which were symptomatic. In all, eleven patients receiving dexamethasone had epigastric discomfort, five had a demonstrable ulcer, and one had a haematemesis, although three preceding radiographs had been normal. The author concludes that the incidence of peptic ulcer after dexamethasone therapy is no greater than after treatment with prednisone, methylprednisolone, or triamcinolone. There is a suggestion that the incidence of ulcer is greater when the patient is receiving a larger dosage of the steroid.

The final conclusion is that in the treatment of S.L.E

dexamethazone is as effective therapeutically as the other steroid preparations previously tried, but that it produces an appreciably higher incidence of side-effects, particularly pitting oedema and insomnia, and for this reason, it is not to be preferred to other steroids.

R. E. Tunbridge.

Familial Occurrence of Systemic Lupus Erythematosus. MARLOW, A. A., PEABODY, H. D., JR., and NICKEL, W. R. (1960). *J. Amer. med. Ass.*, **173**, 1641. 11 refs.

From the Mercy and County Hospitals, San Diego, California, the authors report four well-documented cases of systemic lupus erythematosus (S.L.E.) occurring in two sisters of Italian ancestry and in a mother and her married daughter of Mexican origin. The fifteen previously reported cases of S.L.E. showing a familial incidence are briefly reviewed. [The authors do not attempt to explain the relationship.] *R. E. Tunbridge.*

Roentgen Manifestations in Progressive Systemic Sclerosis (Diffuse Scleroderma). GONDOS, B. (1960). *Amer. J. Roentgenol.*, **84**, 235. 8 figs, 34 refs.

Diffuse scleroderma is a progressive disease of connective tissue which leads to prolonged disability and is often fatal. Any organ may be affected, the sequence of events being always the same—oedema, followed first by connective-tissue proliferation and sclerosis of collagenous bundles, and finally by atrophy. In this report from the General Hospital, Washington, D.C., the author reviews 25 cases seen over the last 16 years and considers the radiological changes encountered in the light of accounts in the literature.

The heart is often enlarged and triangular with diminished pulsation, and at necropsy the cardiac muscles show irregular areas of fibrosis not related to disease of the coronary arteries; the heart was affected in eight of the present cases. In the lungs, affected in seven cases, there is diffuse interstitial infiltration with degenerative cystic lesions; these may expand into pneumatoceles and their rupture may cause a pneumothorax. The author considers this pulmonary fibrosis to be a primary manifestation of the disease. The alimentary tract was involved in fourteen cases, this being characterized by dilatation and decreased intestinal peristalsis, with delay in transit of barium. Such changes are most common in the oesophagus; they were also observed in the small intestine and colon, but no striking abnormalities were seen in the stomach. Bone abnormalities, present in six cases, frequently resulted in absorption of the terminal phalanges of the fingers and, less commonly, those of the feet. Similar changes were noted in the distal ends of the radius and ulna. Attempted remodelling during quiescent phases may produce a conical deformity of the affected bone ends. The presentation of the disease by joint symptoms may be attributed to involvement of synovial membranes. Skin contractures often result in subluxations and dislocations of the interphalangeal and metacarpo-phalangeal joints. Calcinosis of the soft tissues was also observed four times in the present series. Marked thickening of the periodontal membrane, when this occurs provides a strong radiological indication of the disease *R. O. Murray.*

Ophthalmological Manifestations of Collagen Disease. (Les localisations ophtalmologiques des collagénoses.) LASCO, F., and NICOLESCO, M. (1960). *Arch. Ophtal.*, **20**, 602. 4 figs, 75 refs.

The authors have summarized the various ophthalmological manifestations of the collagen diseases, emphasizing the importance of these signs in diagnosis and prognosis.

In periarteritis nodosa, small deep choroido-retinal foci are found, associated with micro-aneurysms, haemorrhages, and cotton-wool exudates. Bilateral, symmetrical retinal detachments are sometimes seen, in some cases early in the disease. Occlusion of the central retinal artery and primary optic atrophy are rare complications. As a result of cardio-vascular or renal involvement, a typical retinopathy may complicate the picture.

Temporal arteritis is frequently the only manifestation of generalized arterial involvement. Pseudo-papilloedema is the most common manner in which it presents, other signs being retrobulbar neuritis and primary or secondary optic atrophy. Occlusion of the central artery of the retina is a less common presenting sign.

Lupus erythematosus may present with superficial or deep retinal haemorrhages, areas of choroiditis, papilloedema, or aneurysmal or obliterative aterial lesions.

Serum sickness may also be associated with a retinopathy of a collagen type.

Dermatomyositis is rarely associated with a late exudative retinopathy.

In generalized scleroderma a retinopathy is not seen, but lagophthalmos sometimes occurs and cataract may form. *B. Jay.*

Neurotrophic Lesions of the Vascular Membrane of the Eye in Scleroderma *en coup de sabre*. [In Polish.] SEGAL, P., JABLÓNSKA, S., and MRZYGLÓD, S. (1960). *Klin. oczna*, **30**, 381. 6 figs, 29 refs.

A case of linear scleroderma *en coup de sabre*, with ipsilateral atrophic iris lesions, is described. The morbid process appeared a few months after severe psychic troubles and the eye lesions developed within several months. Their character showed their neurotrophic origin, which is especially distinct in linear scleroderma. The authors believe that linear scleroderma *en coup de sabre* is not identical with spontaneous Romberg's atrophy, although both those morbid processes show a distinct connexion with the nervous system.

W. H. Melanowski.

Collagen Diseases—Unanswered Questions on Pathogenesis and Aetiology. KAMPMEIER, R. H. (1960). *Arch. intern. Med.*, **106**, 753. 11 figs, 43 refs.

Periarteritis Nodosa in an Infant. (Périartérite noueuse

chez le nourrisson.) MARIE, J., HENNEQUET, A., WATCHI, M., and SZEPETOWSKI, G. (1961). *Ann. Pédiat.*, **37**, 26. 7 figs, 21 refs.

Eye Changes in Periarteritis Nodosa. (Øjenforandringer ved Periarteritis Nodosa.) SVANE-KNUDSEN, P. (1961). *Ugeskr. Laeg.*, **123**, 229. 15 refs.

Experimental Contribution to the Characterization of the L.E. Factor. (Experimenteller Beitrag zur Charakterisierung des L.E.-Faktors.) SPIEGELBERG, H. (1960). *Acta haemat.* (*Basel*), **24**, 330. 3 figs, 15 refs.

Investigations regarding Changes in the Peripheral Blood Picture in Lupus Erythematosus. DUMITRIU, R., DĂNILĂ, P., and POROJAN, I. (1960). *Rum. med. Rev.*, **4**, 55.

Neuraminic Acid and Polysaccharides in the Serum Protein Fractions in Collagen Diseases (Scleroderma and Lupus Erythematosus). (Kwas neuraminowy i wielocukry we frakcjach białkowych surowicy w tzw. kolagenozach (twardzinie i liszaju rumieniowatym). DŻUŁYŃSKA, J., JABŁOŃSKA, S., MAZURKIEWICZ, W., and PIEKARSKA, Z. (1961). *Pol. Tyg. lek.*, **16**, 1. 8 figs, 31 refs.

Psychosis associated with Lupus Erythematosus Disseminatus. LIEF, V. F., and SILVERMAN, T. (1960). *A.M.A. Arch. gen. Psychiat.*, **3**, 608. 8 refs.

Avascular (Aseptic) Bone Necrosis associated with Systemic Lupus Erythematosus. DUBOIS, E. L., and COZEN, L. (1960). *J. Amer. med. Ass.*, **174**, 966. 4 figs, 10 refs.

Non-Articular Rheumatism

Treatment of Scapulo-humeral Periarthritis by the Periarticular Injection of *D*-1-Methylysergic Acid (UML 491). (Tratamiento de la periartritis escapulohumeral por la inyeccion periarticular de butanolamida del acido D-1 metil-lisergico (UML 491).) MORENO, A. RUIZ (1960). *Arch. argent. Reum.*, **23**, 91.

Treatment of Scapulo-humeral periarthritis with Chloroquine. (Klorokin-behandling af periarthrosis humeroscapularis.) ERLENDSSON, F. (1961). *Ugeskr. Laeg.*, **123**, 95. 2 refs.

Studies of the Painful Shoulder (Scapulo-humeral Periarthritis). II. Traumatic Ruptures of the Rotator Cap: A Clear-cut Anatomo-clinical Form of Periarthritis of the Shoulder. (Études sur l'épaule douloureuse [Périarthrite scapulo-humérale]. II. Les ruptures traumatiques de la coiffe des rotateurs: Une forme anatomo-clinique bien précise de la périarthrite de l'épaule.) DE SÈZE, S., RYCKEWAERT, A., CAROIT, M., HUBAULT, A., POINSARD, G., RENIER, J. C., and WELFLING, J. (1960). *Rev. Rhum.*, **27**, 443. 16 figs.

General Pathology

Precipitating Factor for Aggregated Gamma-Globulins in Normal Sera. TARANTA, A., WEISS, H. S., and FRANKLIN, E. C. (1961). *Nature* (*Lond.*), **189**, 139. 2 figs, 9 refs.

The rheumatoid factor of rheumatoid arthritic sera is known often to form a precipitate with aggregated gamma-globulins (A.G.G.). A preparation of A.G.G. of F.II human serum fraction was made and all sera from 200 patients with various diseases and eighty healthy subjects were found to form a precipitate with it, with the exception of sera from ten new-born babies, whose mother's serum was positive. Investigations were made as to the relationship of complement to this precipitation reaction. Decomplementation of a serum by admixture with an heterologous antigen and antibody prevented precipitation with A.G.G. In the precipitation reactions the supernatants showed a decrease in titre of complement up to the point of maximal precipitation, but increased again beyond this zone despite the anti-complementary effect of A.G.G. itself. At least one step in the reaction had a dependence on temperature. Fractional inactivation of the components and of end-piece and mid-piece of complement suggested the possible identity of precipitating factor for A.G.G. with the first component. Since fixation of the first component is known to require calcium ions and to be inhibited by the chelating agent sequestrin, quantitative precipitations were made with a serum containing 0·01 M. sequestrin. The precipitate was thereby increased, while the anti-complementary action of the supernatant was decreased but not completely inhibited. "These findings indicate that the precipitating factor, although suggestively similar to the first component of complement, is distinct from it as well as from the other hitherto known components of complement." Recovery from the precipitate of a globulin entity having a sedimentation constant of S_{20} 10·5 was made by centrifugation, and which entity again formed a precipitate with A.G.G.

Harry Coke.

Latex Slide Test in Rheumatic Disorders. WILSON, J. V., MORISON, R. A. H., and WRIGHT, V. (1960). *J. clin. Path.*, **13**, 453. 1 fig., 16 refs.

This paper from the Royal Bath Hospital, Harrogate, Yorks, records another satisfactory experience with the simple slide test utilizing the commercial preparation of latex particles coated with a globulin for the diagnosis of rheumatism. The results, which were read macroscopically at one minute, were compared with those of the differential agglutination (D.A.) test. Of 603 sera examined, 232 gave a positive result by the latex slide (L.S.) test, and of these only four failed to give a positive D.A. reaction, which is defined as a differential titre of 1:16 or greater. No serum giving a positive D.A. reaction failed to give a positive L.A. test result. After clinical classification, 85 per cent. of those classified as "definite or probable" rheumatoid arthritis gave positive

L.S. test results, while of those classified as "possible" rheumatoid arthritis 44 per cent. did so. The incidence of false positive reactions was assessed at 3·8 per cent. in cases without any suggestion of rheumatoid arthritis, and at 5·3 per cent. in those of osteoarthrosis. Only occasional positive reactions were obtained in the sera of patients with such conditions as ankylosing spondylitis, Still's disease, and psoriasis with arthritis. The percentage of positive results was lower in early cases, in long-standing cases, and those in which the arthritis was "mild in extent". In relation to clinical activity of the disease 88 per cent. of those with active disease gave a positive result, as compared with 54 per cent. of those with inactive disease. No correlation was found between L.S. test results and disease activity as measured by the erythrocyte sedimentation rate or haemoglobin level, but positivity was related to the radiographic bone changes and the presence of nodules. The test is shown to be simple to perform, easy to read, and qualitatively as satisfactory as the more extensive and time-consuming erythrocyte agglutination methods.

Harry Coke.

Rheumatoid and "Non-specific" Sensitivity of the Latex-Fixation (R.A.) Test. (Sensibilità reumatoide ed "aspecificità" della reazione latice-goccia (R.A. Test).) PINTO, L. (1960). *Reumatismo*, **12**, 218. 15 refs.

Latex Reaction. Application to the Study of 1,150 Sera. (La réaction au latex. Application a l'étude de 1,150 sérums.) ARON, E., VARGUES, R., and LECHEVALLIER, P.-L. (1961). *Presse med.*, **69**, 54. 30 refs.

Sensitizing Factor in the Waaler Test. ULSTRUP, J. C. (1960). *Acta path. microbiol. scand.*, **50**, 447. 5 refs.

Anti-hyaluronidase Activity as an Explanation of the Action of Antirheumatic Drugs. (Kann die Wirkung antirheumatischer Pharmaka über eine Hyaluronidasehemmung erklärt werden?) VOGEL, G., UEBEL, H., and MAREK, M.-L. (1960). *Z. ges. exp. Med.*, **134**, 1. 2 figs, 9 refs.

Role of Hyaluronic Acid and Chondroitin Sulphate in Articular Rheumatism and the Possibility of Influencing their Metabolism by Means of Mud Baths. (Uber die Rolle der Hyaluronsäuren und der Chondroitinsulfate beim Gelenkrheumatismus und über ihre Beeinflussarbeit im Stoffwechsel durch Moorbäder.) AMREICH, I. (1961). *Wien. med. Wschr.*, **111**, 7. 10 refs.

Skin Test for the Diagnosis of Rheumatoid Activity. (Un test cutaneo per la diagnosi di attività reumatica.) RUBBIANI, V., and MATTIOLI, G. (1960). *Reumatismo*, **12**, 221. 23 refs.

Behaviour of Synovial Tissue in Rheumatoid Arthritis. (Comportamento del tessuto sinoviale nell'artrite reumatoide.) ORABONA, M. L., SEMERARO, V., and BIANCHI, P. (1960). *Reumatismo*, **12**, 336. 21 figs, 22 refs.

Physiopathology of the Synovial Fluid. (Fisiopatologiá del líquido sinovial.) BORRACHERO, J. (1960). *Rev. esp. Reum.*, **7**, 567. 11 figs, 3 refs.

Immunohistochemical Interaction of Autologous Rheumatoid Serum with Subcutaneous Rheumatoid Nodules. TAYLOR, H. E., and SHEPHERD, W. E. (1960). *Lab. Invest.*, **9**, 603. 3 figs, 16 refs.

Interactions between Red Cells coated with Incomplete Anti-D and Rheumatoid Sera. HARBOE, M. (1960). *Acta path. microbiol. scand.*, **50**, 383. 4 figs, 21 refs.

Electrophoretic Studies of Serum Proteins in Cyanogum Gel. HERMANS, P. E., MCGUCKIN, W. F., MCKENZIE, B. F., and BAYRD, E. D. (1961). *Proc. Mayo Clin.* **35**, 792. 5 figs, 25 refs.

Studies on the Change of Blood Cell Phosphatase Reaction in Rheumatoid Arthritis. NAKAO, T. (1960). *Kumamoto med. J.*, **13**, 236. 4 figs, 13 refs.

Behaviour of the Glycoproteins of Euglobulin in the Serum in Rheumatoid Arthritis and other Diseases. (Il comportamento dei glicoprotidi euglobulinici del siero nell'artrite reumatoide ed in altre forme morbose.) COLOMBO, B., GADALETA, G., and BONOMO, E. (1960). *Reumatismo*, **12**, 324. 43 refs.

Severe Haematological Disorders in Rheumatoid Practice. (Cuadros hemopáticos graves en la enfermería reumatológica.) MORCILLO HERVÁS, C. (1960). *Rev. esp. Reum.*, **7**, 579.

Bacterial Antigens (Tuberculous and Streptococcal), Cartilaginous Tissue and Rheumatic Inflammation. (Antigeni batterici (tubercolari e streptococcici), tessuto cartilagineo e flogosi reumatica.) TESI, A., and ZINI, F. (1960). *Reumatismo*, **12**, 355. 2 figs, 37 refs.

Urinary Excretion of Amino Acids in Rheumatic Diseases. LANDTMAN, B., and VISAKORPI, J. K. (1960). *Ann. Paediat. Fenn.*, **6**, 299. 2 figs, 19 refs.

Tissue Mast Cells in Renal Diseases. PAVONE-MACALUSO, M. (1960). *Acta path. microbiol. scand.*, **50**, 337. 7 figs, 27 refs.

ACTH, Cortisone, and Other Steroids

Combination of Prednisone with Phenylbutazone in the Treatment of Rheumatic Conditions. (L'association fixe de prednisone et de phénylbutazone (G 31109) en pratique rhumatologique.) MEYER, E., THEVENOZ, F., FALLET, G. H., and MARTIN, E. (1960). *Rev. Rhum.* **27**, 313. 36 refs.

This paper from the University Medical Clinic, Geneva, reports the results of treatment of 250 cases of various types of "rheumatism" with tablets containing 50 mg. phenylbutazone and 1·25 mg. prednisone. Previous work on this combination of drugs is described. There was no control group, but the criteria of improvement were laid down before the start of treatment. By these, improvement occurred in from 50 to 75 per cent. of cases of osteo-arthritis of the limbs, periarthritis of the shoulder, non-articular rheumatism, low back pain, and rheumatoid arthritis. On the other hand little benefit was obtained in sciatica and cervical osteo-arthritis, especially the chronic forms of these. The average daily dose was between two and six tablets a day. Side-effects, which were minimal, included three cases of skin irritation, several of minor gastric upset, and one case of reactivated duodenal ulceration. It was found that some cases could be treated with these tablets for as long as 11 months. *G. S. Crockett.*

Treatment of the Dermatoses with 6-Methyl-Prednisolone (Über Erfahrungen mit 6-Methyl-Prednisolon bei Dermatosen.) KNOTH, W., and GÖBEL, B. (1960). *Derm. Wschr.*, **142**, 801. 35 refs.

From the University Skin Clinic, Giessen, Germany, comes this report on the efficacy of treatment with 6-methylprednisone of 62 patients, most of whom were suffering from such conditions as eczema, psoriasis, dermatomycosis, and urticaria, while a few had primarily dermal diseases such as systemic lupus erythematosus and sarcoidosis. The duration of therapy ranged from 10 to 74 days (average 23 days) and the total dose of the steroid from 80 to 2,384 mg., the dosage depending largely upon the type and severity of the disease in each case. Investigations carried out before and during therapy included determination of blood pressure, blood sugar and serum protein and electrolyte levels. There appeared to be no major alterations in any of these values as a result of the therapeutic regimen, except that the serum potassium level was lowered in eighteen cases. However, only one patient, in whom this level was 13·6 mg. per 100 ml., developed symptoms. There was a general increase in the feeling of well-being and no important complications occurred. The dosage of methylprednisone was between 50 and 75 per cent. of that of prednisolone, while it was considered that the former was more easily utilized. The importance of supplementary potassium therapy is emphasized. *Allene Scott.*

Study of the Adrenal Response to ACTH after Prolonged Treatment with Prednisone Alone or in Combination with ACTH or Testosterone. (Étude de la réponse surrénalienne a l'A.C.T.H. après traitement prolongé par la delta-cortisone associée ou non a l'A.C.T.H.-retard ou à la testostérone.) BERTRAND, J., MAITRE-PIERRE, J., and LORAS, B. (1960). *Rev. franç. Ét. clin. biol.*, **5**, 684. 7 figs, 40 refs.

It is known that after prolonged treatment with corticosteroids the adrenal cortex responds subnormally to stimulation with ACTH (corticotrophin). The experiments reported in this paper from the Institut Pasteur, Lyons, were designed to determine the duration of this insufficiency and whether it could be prevented or reduced by including ACTH or testosterone in the therapeutic regimen. The plasma 17-hydroxycorticosteroid levels were first determined at 0, 2, 4, and 6 hours during the intravenous infusion of 25 mg. ACTH in 33 healthy subjects, thus establishing the normal response to such an infusion of ACTH.

A similar infusion of ACTH given to 34 patients 12 hours after cessation of treatment with prednisone alone for various periods, ranging from 20 days to 10 months, gave a uniformly subnormal response. When the test infusion was delayed for 36 hours after cessation of treatment with prednisone, four out of six patients gave a subnormal response, but when 60 hours were allowed to elapse before the test infusion, three out of six patients gave a subnormal response. In a third group of six patients only two gave a subnormal response when 6½ days were allowed to elapse between cessation of treatment and the test infusion, while of six patients who received 15 to 20 mg. prednisone daily for periods ranging from 19 days to 3½ months supplemented by 50 mg. testosterone every 5th or 7th day all gave a subnormal response to the test infusion of ACTH given at 12 hours. However, when treatment with prednisone was supplemented with 20 mg. ACTH-zinc (a retard preparation) every 5th or 7th day, the response to the test 12 hours after cessation of the treatment was normal in four out of six patients. *P. A. Nasmyth.*

[An English translation of this paper was published simultaneously in the U.S.A. (*J. Pediat.*, 1960, **57**, 471). No acknowledgment of this fact is made in either journal. —EDITOR, *Abstr. Wld. Med.*]

Action of ACTH, Cortisone, and Prednisone on the Connective Tissue of Normal and Sclerodermic Human Skin. MANCINI, R. E., STRINGA, S. G., and CANEPA, L. (1960). *J. invest. Derm.*, **34**, 393. 36 figs, 23 refs.

At the Facultad de Ciencias Medicas, Buenos Aires, Argentina, the authors have studied the action of ACTH (corticotrophin), cortisone, and prednisone on human skin. For this they used skin from six healthy volunteers, and from thirty patients with local diseases capable of temporary improvement on hormone therapy. The three hormones were administered parenterally and by mouth, and hydrocortisone ointment was applied locally.

The results obtained in both normal and diseased skin were constant. Normal skin showed progressive atrophy of the collagen bundles and fibres, thinning and

fragmentation of the reticular and elastic fibres, and disappearance of the interfibrillar mucopolysaccharides. The basement membrane appeared to become thin and lose its continuity, while the periodic-acid-Schiff reaction became weaker. Fibroblasts lost nucleoprotein granules from their cytoplasm and the nuclei were pyknotic. In scleroderma and scleroedema adultorum the hypertrophied collagen bundles and the elastic tissues became dissociated, the zones of hyalinization became reduced, and the mucopolysaccharide in the papillary corium disappeared. The glycoprotein, the reticular fibres of the basal membrane, and the hyalinized arterioles were unchanged. Fibroblasts seemed less hypertrophied and lost their cytoplasmic nucleoproteins. Some mast cells lost their granules. All these changes seemed to reach their peak about 4 weeks after treatment, and appeared more marked with prednisone than with corticotrophin or cortisone. The changes were apparently reversible, as the skin returned to normal when administration ceased.

[This paper is illustrated with extremely clear plates.]

G. B. Mitchell-Heggs.

Possible Explanation for Cushing's Syndrome associated with Adrenal Hyperplasia. NUGENT, C. A., EIK-NES, K., KENT, H. S., SAMUELS, L. T., and TYLER, F. H. (1960). *J. clin. Endocr.*, **20**, 1259. 5 figs, 17 refs.

Cushing's syndrome associated with bilateral adrenal hyperplasia can be satisfactorily explained by supposing that it results from an increased secretion of adrenocorticotrophic hormone (ACTH). However, it has not been possible to demonstrate a measurable increase in blood concentration of ACTH in such patients, and it has therefore been doubted that this is the explanation of the syndrome. In an investigation at the University of Utah College of Medicine, Salt Lake City, the effect on the plasma 17-hydroxycorticosteroids of infusing amounts of ACTH insufficient to produce a measurable rise in the plasma levels of the hormone was determined in seven normal young men. The amount of ACTH to be infused in each individual was determined by measuring the maximum quantity which could be infused intravenously for the 4 hours from 8 a.m. to noon without causing a rise in the plasma 17-hydroxycorticosteroid concentration. This was found to range from 1·5 to 5 i.u. per day. The appropriate concentration of ACTH was then infused constantly for 4 days. In two of the subjects 1 mg. dexamethasone was given orally every 8 hours to suppress endogenous ACTH. In four of the seven subjects, and including the two given dexamethasone, the plasma 17-hydroxycorticosteroid level was raised during the 4-day infusion. In five of the subjects the response of the plasma 17-hydroxycorticosteroid level to maximal stimulation with ACTH 2 hours after completion of the 4-day infusion was greater than it was when the same test was made before the infusion. It was concluded that the absence of a measurable increase in blood ACTH concentration in Cushing's syndrome associated with adrenal hyperplasia is not a valid objection to the hypothesis that the condition is due to a constant secretion of ACTH. *P. A. Nasmyth.*

Adrenocortical Function after Long-term Corticoid Therapy. CARREON, G. G., CANARY, J. J., MEYER, R. J., and KYLE, L. H. (1960). *J. Lab. clin. Med.*, **56**, 235. 6 figs, 24 refs.

Prolonged suppression of adrenocortical function is observed after cessation of long-term glucocorticoid therapy. The reactivation achieved by administration of adrenocorticotrophic hormone (ACTH) may not be maintained when treatment is discontinued. In this paper from Georgetown University School of Medicine and Georgetown University Hospital, Washington, D.C., a study is reported of the urinary excretion of 17-ketosteroids and 17-hydroxysteroids in three patients who had received long-term glucocorticoid therapy. The first patient had rheumatoid arthritis for 22 years and had been receiving 50 to 75 mg. cortisone daily for the preceding 7 years. Liver and kidney function were normal but for 3 days following the abrupt withdrawal of corticoid therapy steroid excretion was below normal. A standard 8-hour infusion of ACTH at the end of this short withdrawal period produced an increase in the excretion of 17-ketosteroids and 17-hydroxysteroids, but the response was subnormal. Sustained stimulation with intramuscular ACTH gel resulted in a urinary excretion of 17-hydroxysteroids which was above the normal level, but excretion of 17-ketosteroids although increased, barely reached normal levels. When stimulation was discontinued the output of steroids fell below normal and 11 days after sustained stimulation there was a subnormal response to the standard ACTH test. A similar study was carried out in two other patients who had been receiving cortisone for 2½ and 3 years, respectively. The results were almost identical with those obtained in the first patient, but in these last two patients a longer time was allowed to elapse between withdrawing corticoid therapy and beginning sustained stimulation with intramuscular ACTH gel. The maximum time between withdrawal and sustained stimulation was 7 days and during this time there was no evidence of a spontaneous return to normal excretion of 17-hydroxysteroids or 17-ketosteroids. Only one of the three patients gave an adequate response to the 8-hour ACTH test 10 days after stopping sustained stimulation with intramuscular ACTH gel. *P. A. Nasmyth.*

Peptic Ulcer in Rheumatoid Arthritis and Relationship to Steroid Treatment. BOWEN, R., JR., MAYNE, J. G., CAIN, J. C., and BARTHOLOMEW, L. G. (1960). *Proc. Mayo Clin.*, **35**, 537. 10 refs.

An investigation was carried out at the Mayo Clinic to determine the incidence of peptic ulceration in patients with rheumatoid arthritis and the effect, if any, which steroid therapy has on this incidence. A total of 2,114 patients in whom rheumatoid arthritis was diagnosed in the 2 years 1954 and 1957 were divided into two groups:

(1) 1,237 patients who had received systemic steroid therapy;
(2) 877 who had not been given such treatment.

In addition, a number of patients in Group 1 who had clinical signs of hypercortisonism as a result of treatment were separately studied. The ages of the majority

of the patients ranged from 40 to 69 years, but 49 patients were aged under 10 and 18 over 80. The authors note that in 1947—before steroids were available—23 (3·3 per cent.) of 830 patients with rheumatoid arthritis had peptic ulcer. In 1954, of 627 arthritics given steroids 42 (6·7 per cent.) had peptic ulcer compared with 34 (6·8 per cent.) of 501 not so treated. In 1957, the figures were 51 (8·4 per cent.) of 610 and 37 (9·8 per cent.) of 376 respectively. In the subgroup of 331 treated arthritics with hypercortisonism the incidence of peptic ulcer was 5·7 per cent. in 1954 and 9·9 per cent. in 1957. Of 93 steroid-treated patients with ulceration seventeen (18·3 per cent.) had a gastric ulcer, while in the 71 patients with ulceration not so treated five (7 per cent.) had gastric ulcer. Of a group of 65 patients given intra-articular injections of steroids in 1954, two had peptic ulcer, and of 44 so treated in 1957, four had peptic ulcer. In all six cases the ulcers had been present before treatment started and were not aggravated by it. Of the 1,237 patients treated with steroids, fourteen had severe gastro-intestinal haemorrhage and three had perforation; of the 877 not so treated nineteen had haemorrhage but none had perforation.

The authors quote figures to show that the incidence of peptic ulcer in patients with rheumatoid arthritis seen at the Mayo Clinic and the Massachusetts General Hospital before the introduction of cortisone was 3·3 to 4·7 per cent. In the general population of North America it has been reported to be 1 to 3 per cent., and in England 3·4 per cent. in males and 0·7 per cent. in females. They consider that the most significant finding in their investigation is the increase in the incidence of gastric ulcer—18 per cent. of the peptic ulcers in the steroid-treated patients being gastric as against 7 per cent. in those not so treated. Whether the increase in the incidence of peptic ulceration among arthritics from 3·3 per cent. in 1947 to 8 per cent. for the two years 1954 and 1957 combined is real or is due to better diagnosis cannot be decided. *William Hughes.*

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